MEDICAL LIBRARY

DEC 7 1948

VOLUME LVIII NOVEMBER, 1948 NUMBER 11

THE LARYNGOSCOPE

FOUNDED IN 1896
BY
MAX A. GOLDSTEIN M.D.

PUBLISHED BY
THE LARYNGOSCOPE
640 SOUTH KINGSHIGHWAY ST. LOUIS (10), MO., U. S. A.

NOTICE TO CONTRIBUTORS

THE LARYNGOSCOPE reserves the right of exclusive publication of all articles submitted. This does not preclude their publication in Transactions of the various Societies.

Manuscripts should be typewritten, double spaced, on one side of paper only and with sufficient margins to allow for corrections.

References should be complete: author's surname, initials, title of article, journal, volume, page, month, year.

Six illustrations will be furnished for each article without cost to author. Authors will please limit illustrations to six or assume the expense of additional illustrations.

Proofs will be submitted to authors for corrections. If these are not returned, articles will be published as corrected in this office.

Reprints will be furnished at the following prices:

WITHOUT COVER

	150 Copies	500 Copies	1000 Copies	2000 Copies
Four Pages	$10.25	$12.00	$15.50	$24.00
Eight Pages	20.75	25.75	35.00	52.25
Twelve Pages	31.00	40.00	57.00	89.00
Sixteen Pages	40.50	49.00	65.50	98.00
Twenty Pages	43.00	53.75	79.50	121.00
Twenty-four Pages	58.00	70.50	95.00	143.50
Thirty-two Pages	76.75	91.25	121.25	179.00

WITH COVER

Four Pages	$19.00	$23.75	$33.25	$53.25
Eight Pages	29.50	37.50	52.75	81.50
Twelve Pages	39.75	51.75	74.75	118.25
Sixteen Pages	49.25	60.75	83.25	127.25
Twenty Pages	56.75	70.50	97.25	150.25
Twenty-four Pages	66.75	82.25	112.75	172.75
Thirty-two Pages	85.50	103.00	139.00	208.25

Express charges to be paid by consignee.

THE
LARYNGOSCOPE.

VOL. LVIII NOVEMBER, 1948. No. 11

NIELS STENSEN (NICOLAUS STENO), 1638-1684.

A Famous Anatomist Who Exchanged the Scalpel for a Bishop's Mitre.

WALTER A. WELLS, M.D.,
Washington, D. C.

"One of the strangest figures in all our history," so wrote Sir William Osler, in discussing the "learned Dane" who is the subject of this sketch.

Most biographers have expressed a similar opinion, and have generally applied such words as *strange, singular, unique* in their attempts to describe him. Moreover, they are agreed in the verdict that he was a man of extraordinary mentality.

Sir Michael Foster in his classic, "Lectures on the History of Physiology," said: "This singular man 300 years ago pierced into questions which still move us at the present day."

He was possessed of an amazing versatility and had an extremely checkered career. He changed not only his intellectual pursuit, but also his occupation; not only his occupation but also his religion; not only his religion but also his country; he achieved high rank in the new as in the old.

Having as a youth of but 22 gained immortal distinction by an anatomical discovery, and soon thereafter having made other great medical contributions, he suddenly turned his attention to the problems of a wholly different science, and at once made such revolutionary contributions there that he was regarded as one of the founders of that science.

Editor's Note: This ms. received in Laryngoscope Office and accepted for publication, Sept. 23, 1948.

He then abandoned medicine and general science for theology.

Born a Protestant, brought up in a strict Protestant environment, educated at a Protestant university, he became a convert to the Catholic faith. He then took orders, became a priest and rose to the rank of bishop.

NIELS STENSEN (1648-1686) (from Garrison's History of Medicine).

From the position of personal physician and friend of a munificent prince, we see him translated to the post of missionary in a foreign country.

From a favorite at court, he became an outcast in ecclesiastical circles.

From wealth, popularity and fame he fell into a low estate; and died abroad, deserted, spurned and in abject poverty.

Born and educated in Denmark, he changed his residence first to Holland, then to France and then to Italy and he rose to the highest distinction in each country.

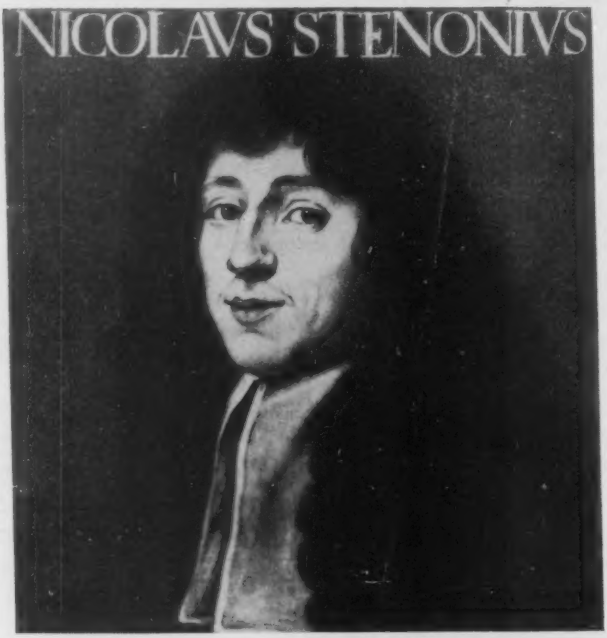

Fig. 1. Portrait of Steno in the Pitti Palace.

He died while serving as missionary in Germany, from where his body was brought to Florence and laid to rest in the tombs of the Medici.

Here, 200 years later, a monument was erected to his memory by the International Society of Geologists. He deserves no less honor from the medical fraternity, but so far no such has been accorded him.

His name, however, has become immortalized in medical literature because of the following eponyms.

Stensen's duct or *Steno's duct* is the universally used name for the duct of the parotid gland. It extends from the anterior end of this gland to a point within the mouth just opposite the second molar tooth.

The parotid gland lies just below and in front of the external ear, and, being the largest of the three salivary glands, may be said to be the chief cause of "mouth watering."

The secretion serves an important function for the beginning of digestion by turning starch element of the food into dextrose.

It is an enlargement of the gland itself that constitutes the chief symptom in an attack of mumps.

Stensen's or *Steno's experiment:* Temporary ligation of compression of the abdominal aorta of an animal, cutting off blood supply in the lumbar region of the spinal cord, and producing a paralysis in the region supplied.

Stensen's or *Steno's foramen,* a y-shaped opening at the anterior part of the intermaxillary suture; foramen incisura.

Stensen's or *Steno's plexus:* A venous plexus surrounding the parotid duct.

Dr. Stensen, as we shall show later, did much to advance medical science otherwise than indicated in these eponyms.

He made notable contribution in the physiology as well as the anatomy of the glands, the muscles and the brain.

It seems strange, therefore, that the usual likeness of him, seen even in medical books, portrays him in a clerical garb. We reproduce here also another less often seen. Looking at these two portraits, you cannot fail to be struck by the contrast which they present. The one is a portrait of him which hangs in the Pitti Gallery at Florence, along with others of the court of Duke Frederick II. He was then personal physician to the Duke, and was at the height of his international fame in medicine and science.

The other is a portrait of him when he was serving as apolistic vicar at Schwerin, his last missionary post.

In the former you see a man evidently full of life, happiness and hope; in the latter you behold a dejected, doleful countenance, one from which the joy of life seems departed. The once celebrated and happy doctor appears to have become a sad and suffering bishop.

Niels Stensen was born at Copenhagen, Jan. 10, 1638, being the son of Steen Pederson, a well-to-do jeweler.

His father having died when he was about six years old, and his mother having remarried, he was brought up in the home of his grandparents. It was, we learn, a very austere household, in which life was strictly regulated by Lutheran principles and practices.

Niels was a sickly child, and one, as he tells us himself, who associated very little with other children, preferring to listen to conversations on religion among his elders.

He was sent to a grammar school, where he proved an apt pupil, especially in languages and mathematics. At the age of 18 he entered the Lutheran-dominated University of Copenhagen.

His chief interest in the beginning was in mathematics, philosophy and languages. He attained an especial proficiency in Hebrew, and was said to be able to read his Bible easily in that language. He became also a good Latin and Greek scholar. He must have had a good training also in other languages, because in later life he spoke fluently Dutch, French, Italian and English.

It was the custom at the university for a student to select one of the faculty to be his special counselor and preceptor throughout the course. Niels selected Dr. Thomas Bartholin, who was a distinguished anatomist. This influenced him to become especially interested in the subjects of biology and anatomy.

It was necessary for a while for him to interrupt all studies. In the year 1658 the city of Copenhagen was besieged and he joined a regiment made up of university students to go to its defense.

When his university term was over, he went to Amsterdam to continue his study of anatomy. This was at the suggestion of Dr. Bartholin, who took great interest in him and observed his special aptitude for the subject. Dr. Bartholin gave him a letter to his friend, Dr. Blaes (Blasius), who had an anatomical laboratory at Amsterdam, where it was thought he would have excellent opportunities for research.

In the middle of the seventeenth century there was general interest in anatomical investigation all over Europe, but in no country so much as in Holland.

An anatomical discovery was a sure road to fame, and the Dutch doctors were in the lead. Indeed, the interest in matters anatomical was not confined to the medical profession. It extended in a great measure to the general population. Evidence of this is to be seen in the number of paintings on the subject which have come down to us from the artists of that era. Among the most famous are Rembrandt's "Anatomy of Dr. Culp," which is one of the masterpieces of the Hague Gallery; Johann von Neck's Anatomy of Dr. Frederik Ruysch," and those of Adrian Baeker on the same subject, to be seen in the Amsterdam Gallery.

Another indication of the general interest — you might say, craze — on the subject was the attention paid to the collection of anatomical specimens. Especially famous was a collection in the possession of Dr. Ruysch, of Amsterdam.

When Peter the Great was a resident of this city, for the purpose of studying modern European ideas and methods, he was a frequent visitor at this museum and before leaving purchased the whole collection at a cost of about $75,000.00.

Dr. Ruysch went immediately to work and made a new equally large collection which he sold to another European monarch for a nearly equal sum.

With Dr. Bartholin's letter in his pocket, Stensen repaired to Amsterdam, where within a few months after his arrival (April 7, 1760), he made the famous discovery of the salivary duct which bears his name; however, he was not permitted immediately to enjoy the honor of this discovery.

Dr. Blaes, who proved to be an incredibly mean and envious person, claimed the discovery as his own, and did everything possible to discredit the young research worker whom he characterized as a malevolent and presumptuous upstart. His claims, however, were generally discounted, even his own brother having admitted that the honor rightly belonged to Stensen.

Naturally disheartened by these developments, Stensen resolved to leave Amsterdam and seek a more favorable environment for his studies, in the famous university city of Leyden; however, even here he failed to escape the animus of Blasius, which persisted and pursued him in his new home.

A letter which Stensen wrote from Leyden to his former preceptor, Dr. Bartholin, is worth quoting here, as giving an interesting account of the discovery, also as an indication of his seemingly sincere modesty of nature.

"Since you urge me in your letter to publish an account of the exterior salivary duct, I am constrained to explain to you briefly the envy which this bit of discovery has won for me, and also the result of this envy; not with the purpose of seeking fame in trifles, but in order to free myself from the hateful charge of stealing what does not belong to me.

"For I am sorry that the necessity has been laid upon me of being forced to say much upon a subject of no importance, or else to submit to the basest brand of shame.

"A due consideration of the matter will show it is not worth making much ado about. For a similar duct had been previously discovered and even the very duct in question had been observed by Casserius, although he called it a muscle. . . .

"Since, however, the charge imputed to me by reason of

that duct does not permit me to keep silent, I shall tell you the entire affair as pupil to preceptor, and shall leave the decision to your judgment. . . .

"It is a year now since I was hospitably received by Blaes. After waiting three weeks for a chance to secure anatomical material, I asked the distinguished man whether I might be permitted to dissect with my own hand such material as I could buy for myself. He gave his consent and fortune so favored me that in the first sheep's head which I bought on April 7th, and was dissecting alone in my room, I found a duct which, so far as I knew, had been described by no one before. I had removed the skin and was preparing to dissect the brain when I decided to examine first the ducts. With this end in view I was exploring the courses of the veins and arteries when I noticed that the point of my knife was no longer closely confined between the tissues, but moved freely in a large cavity, and presently I heard the teeth themselves resound as I thrust my knife forward.

"In amazement at the discovery I called in my host (Blaes), that I might hear his opinion. First he ascribed the sound to the violence of my thrust, then resorted to calling it a freak in nature and finally referred to Wharton.

"But inasmuch as that did not help me and the ducts which had been handled carelessly allowed no further investigation, I decided to examine them another time more carefully. I succeeded, although not so well, a few days later, with a dog's head. Since the affinity to the inferior duct indicated the function of the duct I had found, I told Jacob Henry Paulli, my intimate friend, that I had discovered a salivary duct, and I added a description of it.

"But since I knew something like it had been discovered before and could not determine whether this identical duct had been examined, I remained silent until I could find opportunty to consult Sylvius about it.

"After he had heard my account he determined to seek the duct in man, and having found it he demonstrated it to spectators on several occasions."

Leyden had recently been gaining great renown as a university center. When, about a hundred years earlier, the inhabitants of this city resisted invasion with marked heroism, the king, wishing in some way to show his appreciation, offered the burghers their choice between a remittance of taxes or the establishment of a university. They wisely chose the latter. The university prospered from the start, but never so much as right now.

This was especially true of its medical department, since all the Italian universities, Padua excepted, had closed their doors to non-Catholics. Leyden made no restriction, and it fast became the leading medical center of Europe. The man responsible for its present high prestige was the celebrated Franciscus Sylvius (Franz de la Boe). He was an eloquent lecturer an attractive personality, and he was full of new ideas. He was regarded as the chief exponent of the new school of medical thought, which sought the explanation of all medical processes in chemical reaction and sought cure of all diseases in the use of chemical remedies.

Sylvius, working along this line, made some valuable observations with regard to fermentation and the chemistry of digestion. He made also intensive studies of the anatomy of the brain, with the result that his name has become permanently associated with certain cerebral landmarks (Sylvian fissure, Sylvian aqueduct, etc.). He was, moreover, one of the first to institute regular clinical or bedside instruction of students as an essential part in their medical education.

Stensen soon attracted the attention of the celebrated Sylvius and became one of his favorite pupils.

There were also a number of brilliant students at the university at that time, association with whom must have had a stimulating effect. There was Frederik Ruysch, who was later to became the distinguished professor of anatomy at Amsterdam, and the discoverer of a method of injecting the veins for the preservation of anatomical specimens; there was Jan Swammerdam, who, besides doing the same thing, was one of the pioneers in the use of the microscope (he was the first to

discern and describe the red blood corpuscles) ; and there was Regnier de Graaf, who was to make medical history and his own name famous by the discovery of Graafian follicles. There was also one nonmedical person with whom Stensen became very friendly. This was Baruch Spinoza, who was later to be ranked as one of the world's great philosophers. He lived at the time in a suburb just outside Leyden.

Blasius, as related, persisted in claiming discovery of the parotid duct. He published a pamphlet and wrote letters to his friends on the subject.

Dr. Bartholin made a very curt reply to the letter which he received. "Your conscience," he wrote, "ought to teach you who is right in this matter. Farewell and control yourself."

So far as Stensen, himself, was concerned, the controversy had the effect of stimulating him to further anatomical research, enabling him to confirm not only his previous discovery, but also to make some valuable new contributions. He made a special study of the glands of the eyes, the nose and the mouth, the publication of which still further increased his reputation as a keen and intelligent observer.

In those days questions of anatomical discovery were debated with somewhat the same fervor as questions of religion in the preceding century.

The whole medical fraternity became aroused, everybody took one side or another, and a high degree of animosity was often engendered. It had only been a few years before that a controversy of this kind culminated in a murder.

In 1642, Georg Wirsung, a student of Padua, lost his life as a result of a quarrel growing out of his discovery of the pancreatic duct.

The controversy over the discovery of the parotid duct had now risen to such a pitch that something had to be done about it. The men of learning decided to get together and hear the truth of the matter. So, on June 9, in the year 1661, there gathered together in the assembly hall of the University of

Leyden, the doctors, scientists and others interested, to fully consider the subject. We wish one of the gifted Dutch painters of the era had handed down to us a picture of that scene.

Dr. van Horn, professor of surgery at the university, presided. Seated near him was the great Sylvius, dressed in his robe, a striking figure with his handsome, amiable countenance, his long, curly blond locks falling to his shoulders. Others of the faculty were seated close by: members of the surgeons' guild, richly clad, according to the custom of the time, in their silk and velvet gowns, with high ruffed collars. Sturdy figures, most of these old Dutch doctors with generally somber, stolid features. What a contrast was presented in the slender, delicate Danish youth of only 23, who stood before them, with his pale, sensitive face, his long, sharp nose, his eager, expressive eyes! Naturally close by him was his bosom friend, Jan Swammerdam, whose allowance had recently been discontinued by his father because he preferred pure science to the practice of medicine.

It would be especially interesting if we could have reproduced the face of another fellow-student, Frederik Ruysch, who later on, in the heyday of his glory, was to be the center figure of several famous paintings to be known as "Anatomies." We would like to see Regnier de Graaf, too, as he appeared at that age; also Baruch Spinoza, whose friendship for Niels, as well as his interest in science, were sufficient reasons for his attendance.

All eyes were turned toward the young Dane as he rose to speak, and everybody was impressed by his natural, sincere, straightforward manner, his evident intelligence, his modest but positive assertion.

When through, he had evidently won general approbation and general support. What, however, pleased him most was a letter he received shortly after from his friend and champion, Dr. Thomas Bartholin.

"You are an honor to your country, which rejoices in your

success. Continue my dear Stenius, in the paths of immortal glory which true anatomy holds out to you."

Stensen remained four years at Leyden, and during that time, following the advice of Dr. Bartholin, he continued diligently at work in anatomical research.

He performed experiments on animals to test the effect of ligature or compression of the trunk arteries. One result was a discovery which came to be known as the Stensen experiment.

He made a study of the glands of the eyes, and the mouth, the results of which were published under the title, "Anatomical Observations." His most important work, however, was the study he made of the muscles, including the muscle of the heart. His conclusion produced a sensation, not only in the medical world but also in the world of religion.

"There are those," he wrote, "who consider the heart to be the seat of the soul or even the soul itself, but a close study of this organ convinces us that it is actually nothing else than muscle."

There were many to whom such a blunt statement could not prove otherwise than a considerable shock. This might be so even though they didn't consciously believe the heart to be the soul. It was because for centuries church literature had tended to sanctify the heart — to make it sort of a symbol of spiritual grace.

His conclusion that the heart was purely a muscular structure was a momentous one also for the medical world, for it had been widely believed that it was composed of a special type of tissue or parenchyma peculiar to itself. When Stensen showed that it was made of true muscular fibres and when further he made scientific estimates of the muscular force which it could exert, he did much to confirm Harvey's theory of circulation which was then still in a debatable stage.

A few years later (1669), a great English investigator, Richard Lower, wrote a treatise, elaborating the subject and confirming Stensen's original thesis.

Stensen liked to carry on correspondence, and exchange ideas with other men of learning, living abroad as well as at home.

One of these was Melchisedech Thevenot, a well-to-do naturalist and world traveler, who became interested in this original young scientist and invited him to come to Paris; so, late in 1664, or early 1665, Stensen left Leyden for Paris, where he became a member of Thevenot's household.

Thevenot had made his home the gathering place of distinguished men of learning for the discussion of subjects of interest in science, art or literature. These meetings, indeed, became the nucleus of the Academy of Science which later came into existence, just as the Royal Society grew out of such meetings being held about the same time in private homes in London.

Stensen was immediately recognized as a man of exceptional ability and of stimulating ideas, so he was invited to give a talk on some subject of his own choosing. He took for his subject, "The Anatomy of the Brain." This discourse was published later, and it is regarded as a notable one in the fact that in discussing physiology the author steered clear of the fantastic theorizing usually associated with the subject at that era.

After medical men had lost their faith in the old orthodox doctrines, they seemed to think it incumbent upon them to invent at once some new ones to replace them. This developed into a craze and a number of new theories and systems were advanced to explain the occurrence of disease and to provide a method of cure.

There were at this time three chief prevailing systems to which medical men could give adherence, according to their individual inclination and belief. They were known as the Iatro-chemical, the Iatro-mechanical and the Iatro-mathematical systems. According to the Iatro-chemical school, all the processes of life were the expression of chemical reactions. The leader of the school was no other than Sylvius, the professor of medicine at Leyden.

Sylvius, was, however, not an extremist, and he was perfectly right in his insistence on the ultimate identity of organic and inorganic chemical processes.

Chief among his disciples was Thomas Willis, of Oxford, who made a special study of the brain anatomy and who got his name permanently attached to one of the anatomical features of that organ (Circle of Willis).

The second of these systems, the Iatro-mechanical, was known also as the Iatro-physical. According to its tenets the body was to be regarded simply as a machine, and all its workings are to be fully explained by the laws of physics. It was probably inspired by the recent wonderful discoveries of Galileo and the successful application of physical laws in the advancement of science. The head of the school was Borelli, of Naples, who wrote learned treatises on the physical laws involved in digestion, respiration and locomotion.

A modification of this was designated the Iatro-mathematical. This system was sponsored, as it happens, not by a doctor but by a philosopher and mathematician. Descartes dabbled in medicine as a side issue, and wrote a textbook on physiology which, because of the author's exalted prestige, was widely read and followed. Descartes had great faith in mathematics as the key to unlock every problem. That he thought it might be successfully applied to medical science is revealed by his statement that he had set before himself the problem "whether it be possible to find a medical theory based on an infallible demonstration."

Besides these, there were other systems which had considerable followers. Many clung to some version of the Vitalistic Theories, as propounded by Van Helmont, Stahl and others, the main idea of which is that matter is intimately inhabited by some vital principle (pneuma, anima, archeus) which controls all the processes of nature, and is, therefore, the essential object in treatment.

It was Descartes who first pointed out fundamental differences between mind and matter, in that matter can only be

thought of as divisible and mind as indivisible—a conception that had great influence in checking vitalistic doctrines.

Stensen's discourse on the anatomy of the brain was, as we noted, uninfluenced by any preconceived theory. It was the first discussion of the subject based strictly upon scientific observation, and devoid of metaphysical speculation.

He took occasion to refute several fantastic theories which had been advanced.

Descartes, for example, had come out with the theory that the rational soul was located in the pineal gland, which served, as it were, as a center for all cerebral activities. Stensen had the courage to denounce this notion, as unsupported by anatomical observation. He considered equally as without foundation the opinion of Willis, that intelligence is located in the corpus callosum.

Besides correcting errors, Stensen made some new observations with regard to the ventricles and other structures of the brain, and his treatise has been referred to as the beginning of modern methods of the investigation of this organ.

"If, indeed, the white substance of which I am speaking," he said, "be, as in most places it seems to be, wholly fibrous in nature, we must necessarily admit that the arrangement of its fibres is made according to some definite pattern on which doubtless depends the diversity of sensations and movements." (Discours sur l'anatomie du cerveau, Paris, 1669.)

This was, indeed, a keen observation and a remarkable prescience of the decussation of the pyramids as developed many years later.

The learned Dane made many friends in the literary set of Paris. One of them with whom he contracted a particularly warm friendship was the celebrated pulpit orator, Jacques Bossuet.

It may seem strange that Stensen, with his Lutheran background, would become a close friend of a Catholic divine. It is, however, not more strange than his close friendship with

the Jew philosopher, Spinoza, referred to by a religious contemporary as the author of "the most iniquitous and blasphemous doctrine of which a human being could be capable." Whatever his convictions, Stensen was evidently broad-minded in his affiliation.

Some time in the year 1666 he crossed the Alps for a visit to Italy. He went first for a short stay in Rome, after which he journeyed by way of Leghorn to Florence, the city which was to become his future beloved home for the most of his remaining years.

At Leghorn he lingered for a while in order to occupy himself with the dissection of some of the "denizens of the deep." A dogfish, which he dissected and studied with particular attention, set him on a new train of thought, which, as we shall see, later had important scientific results.

Florence was, at the time, ruled by Duke Frederick II, who was ambitious to revive some of the ancient glory of the Medici. He was a generous patron of learning, and the city had become the gathering place of distinguished persons in art, science and literature. Because of the enthusiastic recommendation of friends, Stensen's position at the court was immediately assured. The Duke chose him as his personal physician, provided him with a residence and a pension, and appointed him to the staff of the Hospital Santa Maria. As we have already seen, Stensen had an extraordinary genus for making friends. Italy in this regard was no exception. The Duke and his household became devoted to him.

Among the eminent Italians who soon became friends of his were Malpighi, the man who discovered the capillaries and thus completed the proof of Harvey's theory of the circulation; Francisco Redi, who made ingenious experiments tending to the overthrow of the then widely believed theory of Spartaneous generation; and Viviani, the talented pupil and friend of Gallileo.

There was one eminent Italian, however, whom he could not count as one of his friends. This was Giovanni Borelli, chief of the Iatro-physicists.

Stensen had done a great deal of work on the anatomy and physiology of the muscles, and shortly after coming to Italy he took up the subject again, but this time from a different angle. In a treatise entitled, "Elements of Myology," published in Florence in 1667, he discussed in detail and with great thoroughness, the physics of muscular action, to correct a widely prevailing error.

It was generally held that contraction took place in the tendon, the fleshy part of the muscle serving, as it were, merely as a sort of packing. Stensen by his keen reasoning came to just the opposite view; he held that the tendon was passive, and that the real muscular force lay in the fleshy part. He had a remarkable conception of the modern view of the contraction of individual muscular fibres. He rejected the idea of animal spirits and he opposed the theory of Borelli, the leading authority of the day, that muscular action was accompanied by a swelling of the muscle due to an influx of fluid conveyed by the nerve.

Borelli, who was an irascible person and could not brook contradiction from any source, greatly resented the stand taken by Stensen, and, as a result of it, became his uncompromising enemy.

Stensen had been in Florence less than a year when an event transpired which was destined to change completely the whole current of his life. It had the beginning, according to the story, in the apothecary shop of the Santa Maria Hospital. This institution, which was founded three centuries earlier by Beatrice Portinari, of Dante fame, was much patronized by the court and the nobility of Florence.

At the head of its apothecary department was a very devout nun, Sister Maria Flavia de Neno, a member of an old aristocratic Tuscan family, who had entered the cloiser 35 years before.

One day, as Dr. Stensen came to the apothecary in connection with his hospital duties, he fell in earnest conversation with the good nun over matters of religion. He was very

much impressed with her piety and intelligence, and she, on her side, with his genius and learning. She forthwith made up her mind that so worthy a man ought not to be outside the fold of the church. To that end she argued for his conversion whenever she saw him and prayed for it, no doubt, when he was away. When, in one of their conversations, he admitted that he was thinking the matter over, much encouraged, she redoubled her energy and enlisted the aid of influential friends in her resolution of bringing him into the church.

The more Dr. Stensen thought about the matter, the more he weakened. Finally he decided to be a Catholic. The stern Lutheran, who had stood firm against the logic of Spinoza and the eloquence of Bossuet, succumbed to the persuasive talk of a cloistered nun. He formally announced his conversion on the day of the feast of Immaculate Conception, Nov. 2, 1667. It is related that on that very day he received from the Danish King an invitation to return to Denmark and become professor of anatomy at the University of Copenhagen.

To hold this post had long been his chief ambition. Now it seemed to have come at a time when it would be impossible. He wrote in reply, informing the King of his change in religion, and suggesting this as a barrier to his appointment. On this account, or some other, the matter was postponed, and nothing was heard of it until several years later. In the meantime, Stensen had found a new occupation for the exercise of his ever active mind.

Ever since he had dissected that dogfish at Leghorn, he could not help thinking of its resemblance to certain formations that had been found buried in the rocks of the earth. He would like very much, he mused, to explore the earth and make a personal study of those curious formations. When he spoke of the matter to the Duke, the latter became interested and offered to provide him with the necessary funds and facilities.

After a few months' serious work, Stensen published the results of his studies in a small book written in Latin, entitled

"De solido intra solidium naturaliter content" (Florence, 1667).

He called it a *"prodromus,"* indicating thereby that he intended later to publish a more complete work, a *"dissertatio,"* but small as it was, the prodromus, as any geologist will tell you, marks a turning point in the science of geology.

The Encyclopedia Britannica, in its biographical sketch of Stensen, completely ignores his medical contribution, and asserts that his fame rests on his "De solido."

"In this notable work," it says, "he describes various gems, minerals and petrefactions (fossils) enclosed within solid rock. He compares fossils with living organisms, and he distinguishes marine and fluviatile formations." His crowning glory is that he was the first person in the world to understand and explain the true nature of animal fossils. Stensen was peculiarly fitted for this work by his anatomical experience. When he saw what resembled shark teeth, embedded in the Tuscan rocks, he was certain that they were the remains of living organisms by their close resemblance to those of the dogfish he had dissected on the shores of Leghorn.

After examining a number of shells, he ventured the statement that even if there were no such thing as living shell-fish in the sea, it was, nevertheless, possible to infer from the internal structure of the fossil shells found in rock that they were remanants of once living creatures.

These thoughts led him to further study, which resulted in the formulation of laws of stratification of the earth's crust, which have since become axiomatic in geological science. He showed that the strata of hills and valleys consist of such material as would naturally be deposited in the form of sediments from turbid waters, and he pointed out the differences between fresh water and sea water formations.

Recently an English version of the Prodromus, with notes, was published by Dr. John G. Winter, of the University of Michigan.

Prof. W. H. Hobbs, in his foreword to this work writes:

"There was no writer upon natural science before the eighteenth century that in accuracy of observation, in cogency of reasoning or in discrimination of judgment, might be compared to the learned Dane. The Prodromus, with minor changes, may be made to harmonize with the science of the twentieth century."

One cannot but wonder whether with his great analytic mind, Stensen might not have had some inkling of the implications of his work, for the upsetting of the orthodox doctrine of his day as to the Biblical flood and the age of the world.

He was, without doubt, aware that it would be a serious matter if church authorities had any such inkling. Bruno was burned at the stake because, among other things, he denied the universal deluge. We know that Stensen took especial pain to affirm that his views were not incompatible with holy scripture. His great influence at the Catholic court of Frederick II was in his favor.

Carrying the indorsements of two eminent scientists, Redi and Viviani, his book received an official church approval.

In the early part of the year 1672, Stensen received, in spite of his change of religion, a renewal of the offer of the professorship of anatomy at the University of Copenhagen. In July of that year he returned to his native city, took up residence with his sister there, and began his professional duties. It turned out, however, to be an uncongenial berth. He had apparently reached a stage where he was more zealous for the cause of religion than of anatomy. As a result he got into religious controversies with some of the uiversity authorities, and his position became so strained that after less than two years he decided to return to Florence. In the meantime, Duke Frederick II had died, and been succeeded by his son, Cosmo III. He was, however, no less hospitably received by the new Duke, who immediately appointed him to take charge of the religious education of his son. In the next three years he devoted himself chiefly to theological studies, and in the year 1675 he became a priest of the church.

He now took upon himself the special duty of converting

others, especially his former co-religionists, to the religion that he had embraced. He got into a spirited controversy with the Minister of Reform at Jena, and he wrote letters to many of his old friends, including the philosopher, Spinoza.

In recognition of these proselyting endeavors, Pope Innocent XI, in 1676, made him a Bishop (Bishop of Titiopolis) and appointed him Apostolic Vicar for Northern Europe.

His first post was at Hanover, in Germany, under the rule at the time, of the Duke of Brunswick, a recent convert like himself; however, the prince, dying shortly after his arrival, was succeeded by his brother, who was a zealous Lutheran.

As the new prince would not tolerate a proselyting Catholic bishop at his court, Stensen soon found it necessary to leave, and he went to Minster. He was not long at Minster before he got into another kind of trouble. This was with certain ecclesiastics of his own religion. He went so far in his protest against the installation of a newly appointed priest that he refused to celebrate mass on the occasion. On account of his disagreement he had now to leave Minster and he went next to Hamburg. Here his trouble with the church increased and grew worse. The fact is, Stensen in his latter years, seems to have relapsed in certain respects to the ideas of his former religion. He was now a bishop of the Catholic religion, and he was supposed to comport himself in a manner commensurate with the state and dignity of that high office. Stensen, however, abhorred anything like ostentation and pomp, especially in religion. He took his missionary duties very seriously, and to him it seemed to call for acts of charity and an attitude of humility. He could not reconcile his mission with the wearing of costly vestments and precious jewelry. He came to believe that what was needed was not an elaborate ritual to appeal to the senses, but rather good works and good example to appeal to the conscience. He pursued a course that not only got him in disgrace with ecclesiastical authorities but brought upon him the fierce hostility of the Catholic laity who, according to account, drove him out of the city, with threats to cut off his ears and even to murder him.

We may get some idea of the extreme asceticism which

marked Bishop Stensen's life at this period, by a letter from a contemporary, quoted by his biographer, Plankers:

"The prelate lived and dressed as though he were the poorest person in the world. His position could only be inferred from his ecclesiastical garb, and even this was only serge, for he would not take the robes of his predecessor, although they were offered to him at a low price, and notwithstanding the Duke made him an ample allowance to enable him to live as became his rank. He gave everything to the poor; for them he sacrificed everything. And he did this as long as we knew him. He even gave the gold necklace with a medallion containing a portrait of the Duke to a friend, with the injunction that it be bestowed upon the poor. When he had nothing else, he sold his silver crucifix and costly bishop's ring to relieve the distress of others."

From Hamburg he went to Schwerin, which was his last post, and where his self-imposed poverty reduced him to a state of abject misery. Here he died, truly a pathetic figure, neglected and spurned by those of his chosen religion. There was one friend, however, who remained steadfast, and that was Duke Cosmo III, of Tuscany, the son and successor of his patron, Frederick II. The Duke arranged to have his body brought back to Florence and buried among the tombs of his own ancestors in the famous Basilica of St. Lawrence.

Dr. Bartholin predicted that his pupil, Niels Stensen, by continuing in the path of anatomy would surely gain immortal glory. In that path he continued long enough to have that prediction come true. Then, straying off into side-path, he won immortal glory for his achievement in the science of geology; but Stensen, not content with the glory that is of earth, struck out on a path that would lead him to glory in heaven; he sought not a worldly but a celestial crown.

Here, too, we cannot believe that he was otherwise than successful; certainly so if, as we are taught to believe, sincerity of purpose and self-sacrifice are the straightest and surest paths leading to such reward.

ANESTHESIA IN ENDOSCOPY.*†‡

JOSEPH W. KING, M.D., Anderson, Ind., and
DAVID H. JONES, M.D., New York, N. Y.

Nearly all forms of anesthesia have been tried in endoscopy, but it is generally agreed that local anesthesia is more efficient because it allows the patient to cooperate and avoids the toxic side effects of general anesthesia. Over a period of two years we have performed 1,182 scheduled endoscopic procedures. This does not include preoperative and postoperative bronchoscopies and bronchograms, for which our usual anesthetic routine was used. Of this number we have used general anesthesia in 24 cases, and the remainder were done under local anesthesia of three different types. In our series we were unfortunate to have had two fatal reactions, which prompted our department to seek a method of local anesthesia both safe and efficient. Dr. S. H. Thaler, Veterans' Administration Chief of the Eye, Ear, Nose and Throat Department, made a survey of anesthetic agents used in other hospitals in the city, but the agent and amount used differed in every instance, and the records of reactions were inconsistent. We felt it would be of value to report our experiences and the methods of anesthesia finally decided upon.

Prior to surgery, each patient is interviewed to determine the degree of apprehension that may be expected, and his physical status is evaluated by a review of the clinical findings and his general appearance. The patient is questioned regarding previous anesthetic reaction. The procedure is explained

---

*Read before the Section on Otolaryngology, New York Academy of Medicine, New York, N. Y., May 19, 1948.

†From the Department of Otolaryngology, Veterans' Administration, New York, N. Y. Dr. David H. Jones.

‡Published with the permission of the Medical Director, Branch Office No. 2, Department of Medicine and Surgery, Veterans' Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

Editor's Note: This ms. received in Laryngoscope Office and accepted for publication, June 16, 1948.

and the importance of cooperation is stressed. On the basis of this interview, the type of premedication and anesthesia is determined.

If a general anesthetic is decided upon, the premedication is determined by the anesthetist. For a general anesthetic, we prefer ether. This is usually given by the open drop method. Of the 24 generals, six were supplemented by intravenous ether in 6 per cent solution. We have found this method very satisfactory.

Premedication for local anesthesia should allay the fears of the patient, reduce the amount of anesthesia needed, decrease bronchial secretions, and counteract the toxic effects of the local anesthesia to be used. We use seconal 0.1 gm. two hours and one hour prior to surgery; morphine 15 mg. and atropine 0.4 mg. 45 minutes prior to surgery. The seconal, a quick acting barbiturate, is valuable in the relaxation required, and is specific for the central nervous system stimulation of cocaine. Morphine is considered by some to increase the toxicity of cocaine, since both are depressants. We feel that this is secondary to its effectiveness in relieving psychic trauma, thereby reducing the total amount of anesthesia needed. Our dosage of morphine is flexible according to the patient's condition, but it is always less than will produce respiratory depression. Atropine is used to decrease bronchial secretions and to relax the bronchial musculature.

For local anesthesia we first used cocaine in combination with pontocaine. The throat was sprayed with 2 per cent pontocaine, then slowly 1 cc. of 2 per cent pontocaine was instilled directly into the larynx, drop by drop, followed by 1 cc. of 10 per cent cocaine instilled in the same manner. This method was used in 607 cases. It produced good anesthesia and could be done quickly. Although accurate records were not kept of mild reactions, an impressive number were observed. There were two severe toxic reactions, necessitating heroic measures to prevent fatalities. There was one death which, although called an anesthetic death, was complicated by hemorrhage following biopsy of a bronchial lesion. The

objection to this method was that it combined two drugs, both toxic. In the event of toxic reactions, it would be difficult to determine whether pontocaine, which can cause death by respiratory failure, or cocaine, which can cause death by both respiratory and cardiac failure, would be the offender. Treatment might be confused. It was decided that a safer local anesthesia should be found.

Dr. David H. Jones, our chief consultant, recommended the use of Forrestier's solution, which he had used for several years without observing any toxic manifestation. Forrestier's local anesthetic is a 1.5 per cent cocaine solution combined with phenol, adrenalin and potassium sulphate in proportions which Forrestier considered to be synergistic with cocaine.

FORRESTIER'S SOLUTION.

Cocaine hydrochloride	2.0
Phenol	0.2
Potassium sulphate	0.2
Adrenalin 1:1000	10.00
Cherry laurel water	40.00
Aqua distilled qs ad	150.00

We modified the original method of Forrestier. The throat was sprayed with the solution, and then with laryngeal syringe, by indirect visualization, 2 cc. were instilled slowly into the larynx. With five-minute intervals between instillations, this procedure was repeated for five doses. This method was used for 238 patients. The anesthesia was satisfactory, and the first 233 procedures were without incident. We then had five consecutive reactions. The first advanced into the convulsive stage, but by use of barbiturates, his symptoms were controlled. There were three mild reactions. In these three, the operative procedure was canceled, but no active treatment was necessary. Two of these patients had been anesthetized before with the same solution without reaction. The fifth case was considered an allergic type of reaction and was fatal. An autopsy was performed, and the findings did not completely agree with the clinical impression of an allergic

reaction. The patient, who was known to have had a compensated cardiac condition prior to surgery, was found, on autopsy, to have had an advanced coronary heart disease severe enough to cause death at any time. No alkaloid of cocaine was found in any of the organs. The Forrestier's solution was sent for chemical analysis and was reported to have contained each of the drugs in the proportion ordered. The five reactions occurred when amounts in excess of the prescribed amount were known to have been used. I personally feel that this anesthetic agent, used in prescribed amounts, is both safe and efficient.

At this time, the Ear, Nose and Throat Department, together with the anesthesia board of the hospital, decided on certain definite procedures for local anesthesia. Preanesthesia remained the same. Pontocaine, because of its known toxicity, five to 10 times that of cocaine, was not to be used. By pharmacological estimate, the minimal lethal dose of cocaine is placed at 0.2 gm. given intravenously. It was decided that a total of 4 cc. of 4 per cent cocaine, a dosage of 0.16 gm. would be used. Adrenalin was not to be added to the solutions because of its tendency to increase the toxicity of cocaine. An emergency kit, containing intravenous barbiturates and cardiac stimulants, was to be kept in readiness, and oxygen was to be available at all times. Sensitivity tests were discussed, and it was the opinion of Dr. E. A. Rovenstine, our chief consultant anesthetist, that most tests were unsatisfactory, and that by observing a five-minute interval between the applications of each cc. of cocaine solution, we would have ample warning of sensitivity. An accurate record of reactions, mild and severe, was to be kept.

The method evolved for local anesthesia in laryngoscopy and bronchoscopy is as follows: the first cc. is instilled by atomizer for pharyngeal anesthesia, intranasally. The patient's extruded tongue is grasped and held. He is instructed to hold his breath while the solution is sprayed and for a few seconds after, then to take a deep breath. By this means, the anesthetic is retained in the nasopharynx and any excess passes into the larynx. After a five-minute interval, 1 cc. is

instilled, with laryngeal syringe, drop by drop, onto the base of the tongue, the valleculae, lingual surface of the epiglottis, the laryngeal surface of the epiglottis, and finally directly into the larynx. With intervals of five minutes, these instillations are repeated for a total dosage of 3 cc.

In esophagoscopy, the pharyngeal spray is used in the same manner and may be sufficient in itself. One cc. of the solution may be instilled in the pyriform sinuses if needed.

Since we have started this new series, we have done 313 procedures without toxic reaction. In only three instances has it been necessary to reschedule the patient for general anesthesia. In three cases, additional spray of 4 per cent cocaine was necessary to achieve anesthesia at lower levels. Gagging, coughing and straining were infrequent, and relaxation was good. Although it is too early to state definitely about the possibility of toxic reactions, our present method is satisfactory from the standpoint of anesthesia. The following table illustrates the type of records we are keeping.

ANESTHESIA RECORD.

Name	Anesthetic Used	Amount	Diagnosis	Op.	Relaxation	Gagging	Coughing	Straining	Remarks
J. H.	Cocaine 4%	4 cc.	Ca. Esoph.	E	+	—	—	—	Good
H. Y.	Cocaine 4%	4 cc.	Bronchial Chondroma	B	+	—	—	—	Good
V. M.	Cocaine 4%	4 cc.	Bronchiectasis	B	—	+	+	+	Poor
W. M.	Cocaine 4%	4 cc.	Laryngeal Polyp	L	+	—	—	+	Fair
J. B.	Cocaine 4%	4 cc.	Asthma	B	—	+	—	+	Failure M. S. contra indicated

In conclusion, there are a few points I would like to stress. First, although the tragedy of fatal reaction in local anesthesia is well known, there seems to be little agreement as to the type and amount of local anesthesia that may be safely and

efficiently used. The deaths that I have reported from the pontocaine and cocaine solution, and the Forrestier's solution, were both questionable on the basis of the autopsy findings. We chose to admit the two deaths as due to anesthesia to emphasize the fact that, in endoscopy, we are forced to carry out anesthetic procedures on seriously ill patients who, because of their inability to properly eliminate toxic agents, may be poor risks. In all instances of reactions where the amount of total dosage greater than that prescribed in our methods was necessary, the amount used did not exceed or even approach that described as necessary for endoscopic procedures by recognized authorities. Where relaxation cannot be achieved by the usual amount of local anesthetic agent, we prefer to reschedule the patient under general anesthetic.

We hope that by our present method, using adequate preanesthesia, low dosage of cocaine, a total of 0.16 gm., the interval method of instillation providing a test for sensitivity, and accurate record of results, we will be able to avoid the catastrophe of severe toxic reactions.

BIBLIOGRAPHY.

1. ADAMS, CHARLES R.: Intravenous Anesthesia.

2. ADRIANI, JOHN: Some Practical Aspects of the Chemistry and Pharmacology of Local Anesthetic Drugs. *South. Med. Jour.*, Feb., 1946.

3. GOODMAN and GILLMAN: The Pharmacological Basis of Therapeutics.

4. MAYER, EMIL: The Toxic Effects Following the Use of Local Anesthetics. *Jour. A. M. A.*, 82:876, 1924.

5. ROVENSTINE, E. A.: Mucous Membrane Anesthesia. Anesthesia Files, V. A. Hospital, Bronx, N. Y.

6. *Veterans' Administration Tech. Bull.*, 10A-106.

7. WHALEN, EDWARD J.: Anesthesia in Peroral Endoscopy. *Ann. Otol., Rhinol. and Laryngol.*, 1944.

267 Citizens Bank Building.
140 East 54th Street.

THE LOCAL APPLICATION OF "SULFAMYLON" [Para-(Aminoethyl)-Benzene Sulfonamide Hydrochloride] IN OTITIS EXTERNA AND CHRONIC OTITIS MEDIA.*

A Preliminary Report of 141 Infections in 108 Patients.

J. W. McLAURIN, M.D.,
Baton Rouge, La.

The numerous therapeutic regimens suggested for the management of otitis externa and chronic otitis media are, as usual, clear proof of the ineffectiveness of any single method of treatment. The introduction of a succession of new drugs has repeatedly seemed to solve the problem, but an adequate trial of each one has invariably brought to light undesirable properties which more than counterbalance any effectiveness it was at first thought to possess.

It is with some hesitation, therefore, that I report the use of a new agent in the treatment of otitis externa and chronic otitis media. Over a nine-month period, however, my results with sulfamylon have been so good that I feel justified in putting on record the 108 patients, 33 of whom had bilateral infections, on whom I have used this drug to date.

My attention was first called to the usefulness of sulfamylon by Clark's[1] report on its effectiveness in the prevention of postoperative infection in ophthalmologic cases. Bacillus pyocyaneus which had formerly proved an extremely troublesome secondary contaminant, was completely controlled in 84 successive cases by the use of sulfamylon in 1 per cent solution for irrigations of the conjunctival sac and for moistening the eye pads used as dressings. Although dressings were changed frequently, and in some cases applications were continued for

*From the Division of Otolaryngology of the School of Medicine of Louisiana State University.

Editor's Note: This ms. received in Laryngoscope Office and accepted for publication, Oct. 6, 1948.

a month after operation, there was no instance in the series of any of the reactions experienced with other sulfonamide preparations. Clark[2] has continued to use sulfamylon with similarly good results.

Sulfamylon [para-(aminoethyl)-benzene sulfonamide hydrochloride] is a crytalline white substance freely soluble in water. It is derived from benzylamine and differs from sulfanilamide in that a methylene group has been inserted between the benzene ring and the 4-amino group.

A number of studies have revealed the effectiveness and innocuousness of sulfamylon. Both Brewer[3] and Domagk[4] showed that its antibacterial activity is not inhibited by p-aminobenzoic acid and that its range of antibacterial activity is, therefore, wider than that of sulfanilamide, sulfathiazole and other sulfa compounds. Brewer's[3] investigations, which were confirmed by Lawrence,[5] showed that sulfamylon is more effective against anaerobes and aerobes *in vitro* than comparable concentrations of sulfanilamide and sulfathiazole. Repeated instillations into the conjunctival sac of rabbits, with solutions ranging from 0.5 to 2 per cent, and into the bladder, with solutions ranging from 1 to 20 per cent, showed that sulfamylon does not harm mucosal tissues.

Howes,[6] after investigating the relative effectiveness of streptomycin, penicillin, parachlorophenol, tyrothricin, zephiran and sulfamylon for local chemotherapeutic application, concluded that of them all, sulfamylon possesses the widest range of antibacterial activity. Its particular advantages are that it is rapidly bactericidal, it is active in the presence of pus and blood, it is not affected by changes in the acidity of the environment, and it is relatively nontoxic.

To date there seems to have been only one report on the use of sulfamylon in otolaryngology. In 1947, Fox[7] reported the treatment by this agent of 137 patients with rhinosinusitis, his results being so good that he concluded that sulfamylon is "the most valuable of the available chemotherapeutic agents in the local treatment of acute rhinitis and sinusitis." Neo-

synephrin was used simultaneously in some of the early cases of acute rhinosinusitis and sulfathiazole or sulfadiazine was used in 13 of the 53 cases of frank empyema of the antrum in the series. Although it is Fox's practice to resort to antrostomy if antral infections do not clear up after three or four irrigations, operation had not been required in a single instance after sulfamylon was added to the therapeutic regimen.

Before sulfamylon was used clinically in the treatment of otitis externa and chronic otitis media, as reported in this communication, a series of cultures was made from material removed from the ears of patients with these conditions, and the *in vitro* effect of the drug was tested on the organisms grown. Blood agar plates and brain veal broth media were used, and solutions were tested in strengths of 0.25, 0.5, 1, 2, 3 and 4 per cent (see Table 1). Without a single exception each

TABLE 1.
IN VITRO EFFECTS OF SULFAMYLON SOLUTIONS ON VARIOUS ORGANISMS IN OTITIS EXTERNA AND CHRONIC OTITIS MEDIA.*

Organism	Culture	Sulfamylon Solution 0.25%	0.5%	1%	2%	3%	4%
Pseudomonas aeruginosa	+	—	—	—	—	—	—
Staphylococcus aureus	+	—	—	—	—	—	—
Beta hemolytic streptococcus	+	—	—	—	—	—	—
Klebsiella pneumoniae	+	—	—	—	—	—	—
Alpha hemolytic streptococcus	+	—	—	—	—	—	—
Escherichia coli	+	—	—	—	—	—	—

*Growth +. No growth —.

of these dilutions inhibited the growth of the organisms, which, it should be noted, are those most commonly responsible for otitis externa and chronic otitis media.

My own experience with sulfamylon includes, as already mentioned, 108 patients and 141 ears. Cultures were made routinely in the first 73 cases (ears), which included 33 instances of external otitis (21 primary, seven secondary to furunculosis, and five secondary to fungous infection); 24 instances of chronic otitis media; nine infections secondary to the fenestration operation; and seven infections secondary

to tympanomastoidectomy. In the majority of cases the cultures revealed pseudomonas aeruginosa, staphylococcus aureus, beta and alpha hemolytic streptococcus, Klebsiella pneumoniae and Escherichia coli. Because of the uniformity of the bacteriologic findings and the effectiveness of sulfamylon against the otitic infections, cultures were not made in the last 68 cases (ears) in this series. In these cases treatment was instituted as soon as the diagnosis was established. This plan is still in effect in my practice.

Treatment is simple. Sulfamylon in 1 per cent solution (which has proved as effective as the 4 per cent solution) is instilled into the affected ear and is allowed to remain five minutes by the clock. The ear is then blotted dry with cotton. This procedure is repeated three times daily as long as is necessary; it is seldom required longer than a week and may be necessary only three or four days.

Sulfamylon was effective in every one of the 141 otitis infections in this series, and was usually promptly effective. In no instance was treatment necessary longer than 14 days, and in 93 cases the infection was controlled by the seventh day. The single reaction in the series was the result of a local allergy. Diagnosis was established by a patch test and the reaction cleared 48 hours after sulfamylon had been discontinued and an antihistaminic drug had been administered.

SUMMARY AND CONCLUSIONS.

After appropriate preliminary *in vitro* bacteriologic investigations, sulfamylon was administered locally to 108 patients with otitis externa or chronic otitis media, which in 33 instances was bilateral. In approximately half of the cases the responsible organisms were identified by culture. In the remaining cases treatment was begun when the diagnosis was established clinically. Sulfamylon proved effective *in vitro* against all the organisms isolated in the preliminary bacteriologic study and was promptly effective in every case in which it was used clinically. The single reaction proved to be the result of a local allergy.

On the basis of this experience, sulfamylon seems more effective in otitis externa and chronic otitis media than any other agent now available.

My thanks are due to Ava Ekert, B.S., M.T., and Mary Digarolama, M.S., M.T., of the technical laboratory staff, Our Lady of the Lake Sanitarium, for their help in the *in vitro* studies reported in this communication.

REFERENCES.

1. Clark, William B.: Local Use of "Sulfamylon" [Para-(Aminoethyl)-Benzene Sulfonamide Hydrochloride]. *Arch. Ophth.*, 38:682, Nov., 1947.

2. Clark, William B.: Personal communication.

3. Brewer, J. H.: Clear Liquid Mediums for the "Aerobic" Cultivation of Anaerobes. *Jour. A. M. A.*, 115:598, 1940.

4. Domagk, G.: The Mode of Action of the Sulfonamides. *Deut. Med. Wchnschr.*, 69:379, 1943; abstracted in *Bull. War. Med.*, 4:300, 1944.

5. Lawrence, C. A.: *In Vitro* Studies on the Antibacterial Actions of Para-Aminomethylbenzenesulfonamide Derivatives. *Jour. Bact.*, 49:149, 1945.

6. Howes, E. L.: Local Chemotherapy of Wounds. *Surg., Gynec. and Obstet.*, 83:1, 1946.

7. Fox, Samuel L.: The Use of Sulfamylon in Rhinosinusitis. *Ann. Otol., Rhinol. and Laryngol.*, 56:946, 1947.

INTERNATIONAL CONGRESS OF OTOLARYNGOLOGY, LONDON, 1949.

The British Association of Otolaryngologists is organizing the Fourth International Congress of Otolaryngology, to be held in London from July 17 to July 23, 1949. There will be further meetings, for those who wish to go, at Oxford, Cambridge and Edinburgh on July 25 and 26. It is hoped that a full academic program will be arranged, and also various social functions.

The secretaries of the National Otolaryngological Societies have been circularized and asked to send a list of their members for individual notification. Should any association not receive this letter, they should communicate with the General Secretary, F. C. W. Capps, F.R.C.S., 45, Lincoln's Inn Fields, London, W.C. 2.

BACTERIOLOGICAL STUDIES ON A NASAL DECONGESTANT CONTAINING THE ANTIBIOTIC METHYLOL GRAMICIDIN.*

BARBARA TAYLOR and MILTON J. FOTER,
Cincinnati, Ohio.

INTRODUCTION.

The value of nasal decongestant preparations in practice is to provide relief from upper respiratory "stuffiness" in such conditions as the common cold, acute catarrhal rhinitis, allergic rhinitis and acute rhinosinusitis. Prompt relief can be obtained most readily for the patient by means of a decongestant spray or nose drop.

The varied symptoms of upper respiratory tract disorders are well known, and the therapeutic aims of local medication in such disorders include the reduction of nasal congestion, promotion or restoration of ciliary function, and the elimination of pathogenic organisms (Heatly, 1936; Tremble, 1947; Pullen, 1947).

Crowe (1943) found treatment of infection to be a major problem in otolaryngology, and Dolowitz (1943) pointed out that most ear and nasal sinus infections are secondary to acute coryza or nasopharyngitis and are due to bacterial invasions, although the primary inciting agent may be a virus. Whalen (1944) states that in the cold sequence the increase in bacterial numbers and virulence is the important phase causing extension of infection to nasal sinuses, the middle ear, or even the blood stream.

Dowdeswell (1942) and Dolowitz (1943), in studies on

*Bacteriology Department, Research Laboratories, The Wm. S. Merrell Co., Cincinnati, Ohio.

Editor's Note: This ms. received in Laryngoscope Office and accepted for publication, Oct. 4, 1948.

coryza patients found the predominant organisms to be species of Pneumococcus, Staphylococcus, Hemophilus and Streptococcus. Other organisms found include Neisseria, diphtheroids and Sarcina. Similar studies have been carried out by Julianelle (1945) and Rumreich (1943). Obviously it is not always feasible to identify the specific organisms in every case of coryza or rhinitis and it is therefore important that any antibacterial agent used have a broad spectrum of effectiveness. It has also been wisely concluded by Dolowitz (1943) that the ideal procedure would be to use bactericidal and bacteriostatic agents locally in minor infections and reserve administration by mouth and by vein for the more serious spreading infections.

Modern knowledge of nasal physiology and new drugs has led to the formulation of an antibiotic nasal decongestant which combines the prime feature of decongestant action with the blended antibacterial activity of an improved antibiotic derivative and a quaternary ammonium salt, but which maintains low toxicity.

The medicament, Vonecidin, contains the decongestant phenyl-propylmethylamine hydrochloride (Vonedrine brand) (2.8 per cent) in an essentially aqueous isotonic solution, combined with 1:10,000 methylol gramicidin (Methacidin brand), the antibiotic derivative, and 1:5,000 cetylpyridinium chloride (Ceepryn brand). Gramicidin is the more active of the two components of tyrothricin and, when reacted with formaldehyde, it becomes methylol gramicidin, a more soluble and less toxic antibiotic derivative (Lewis, 1945). Tyrocidin, representing approximately 60-80 per cent of the mixture tyrothricin, is largely inactive *in vivo* since it is rendered much less active by small amounts of albumin. Gramicidin, which is less toxic than tyrocidin for most tissue cells, appears to inhibit certain metabolic reactions rather than act as a protoplasmic poison, and it therefore retains much of its activity *in vivo* (Dubos, 1942).

It is the purpose of this paper to show that Vonecidin, an aromatized clinically isotonic nasal decongestant, combines low surface tension with a broad antibacterial action resulting

from a compatible mixture of a nontoxic antibiotic derivative and a quaternary ammonium germicide.

Henderson (1946) stated that in general the bactericidal level of gramicidin is very close to the bacteriostatic level.

The formaldehyde derivative of gramicidin reported by Lewis (1945) shows reduced hemolytic properties, a loss in toxic activity, and an antibacterial activity only somewhat less than that of gramicidin. It lowers surface tension and retains its activity in the presence of serum. These features, together with those brought out by Henderson (1946), namely, that the tyrothricin antibiotics are heat stable and are not prone to produce sensitivities, give methylol gramicidin certain advantages over other antibiotics in the formulation of a nasal medicament.

Cetylpyridinium chloride has been established as an effective quaternary ammonium compound with bactericidal properties under such diverse conditions as to make it an exceptionally versatile and valuable germicide (Quisno and Foter, 1946). The results of Warren *et al.* (1942), indicate that for topical application or for wound cleansing, it is essentially nontoxic in the concentrations generally used.

EXPERIMENTAL.

Physical Properties of Vonecidin.

It has been reported by Tremble (1943, 1947) and others that the normal pH of nasal secretion is slightly acid, except during acute sinusitis or allergic rhinitis when the pH is alkaline. Fabricant (1943) has found the approximate range of normal physiologic nasal pH values for humans to be between pH 5.5 and 6.5 as measured directly by glass electrode, and he has suggested the use of appropriate nasal medicament which lowers the abnormal alkaline pH found in certain respiratory conditions. Buhrmester (1938) has stated that a return to normal pH of nasal secretions parallels clinical improvement in cases of upper respiratory infections. Turnbull (1943) reported pH values of 2.5 to 10.0 for seven decongestants.

Readings in this laboratory were made on Vonecidin and two other antibiotic decongestants for pH values. A model G Beckman glass electrode pH meter was used and the value found for one product was 6.25 and for the other, 4.9. The value for Vonecidin is 5.5-6.5.

As indicated by Addison (1947), surface tension of aqueous solutions has long been recognized as one of the more important physical properties controlling wetting and detergent powers. In general, the lower the surface tension the better the wetting power of the liquid, so that aqueous medicaments with low surface tension are able to spread quickly over a large area.

By means of a Du Nouy tensiometer the surface tension of Vonecidin was compared with that of an aqueous solution of cetylpyridinium chloride, methylol gramicidin and two antibiotic decongestants with the results shown in Table 1.

TABLE 1. COMPARATIVE SURFACE TENSIONS OF ANTIBIOTIC DECONGESTANTS AND METHYLOL GRAMICIDIN.

Test Material	Surface Tension in Dynes Per cm. at 25.5° C.
Antibiotic decongestant A	36.2
Antibiotic decongestant B	41.9
Cetylpyridinium chloride (1:5,000 aqueous)	45.9
Methylol gramicidin (1:10,000 aqueous)	52.7
Vonecidin	37.2

Antibacterial Action.

The germicidal action of Vonecidin was evaluated against 16 organisms commonly associated with upper respiratory tract infections. The organisms selected were those found most prevalent and most resistant in everyday practice. Critical killing times were determined for 18 to 24-hour cultures of the test organisms in the presence of serum. To a mixture of 5 ml. of sample and 0.5 ml. of sterile bovine serum was added 0.5 ml. of culture, the temperature being held constant at 37° C. At various time intervals subcultures were made

TABLE 2. ANTIBACTERIAL SPECTRUM OF ANTIBIOTIC DECONGESTANTS WITH 10 PER CENT SERUM.

Test Organism	Vonecidin									Antibiotic Decongestant A									Antibiotic Decongestant B[1]								
	¼	½	¾	1	1½	2	3	4	5	¼	½	¾	1	1½	2	3	4	5	¼	½	¾	1	1½	2	3	4	5 min.
Staphylococcus aureus	+	+	+	+	+	+	+	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	—	—
Staphylococcus albus	+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	+	+	—	—	—	—	—	—	—
Diplococcus pneumoniae, Type I	—	—	—	—	—	—	—	—	—	+	+	+	+	—	—	—	—	—	+	—	—	—	—	—	—	—	—
Diplococcus pneumoniae, Types II, III, VII, VIII	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Streptococcus hemolyticus	—	—	—	—	—	—	—	—	—	+	+	+	+	+	+	+	+	+	—	—	—	—	—	—	—	—	—
Streptococcus viridans	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	+	—	—	—	—	—	—	—	—
Escherichia coli	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pseudomonas aeruginosa	+	+	+	+	+	+	+	+	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Klebsiella pneumoniae, Type A	—	—	—	—	—	—	—	—	—	+	—	—	—	—	—	—	—	—	+	+	+	—	—	—	—	—	—
Klebsiella pneumoniae, Type B	—	—	—	—	—	—	—	—	—	+	+	—	—	—	—	—	—	—	+	+	+	—	—	—	—	—	—
Neisseria catarrhalis	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	+	+	—	—	—	—	—	—
Hemophilus influenzae, Type a	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Hemophilus influenzae, Type b	+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	+	—	—	—	—	—	—	—	—

[1]Contains a quaternary ammonium compound.
+Represents growth, or survival, of the test organism at the time of subculture.
—Represents no growth or killing of the test organism.

with a standard 4 mm. bacteriological transfer loop to a suitable culture broth containing added lecithin and Tween 80 as neutralizing agents for any quaternary ammonium germicide carried over (Quisno, Gibby, Foter, 1946). It has also been found that lecithin and Tween 80 are effective neutralizing agents for methylol gramicidin.

Two other antibiotic (tyrothricin) decongestants, one containing a quaternary ammonium compound, were evaluated along with Vonecidin and the results are presented in Table 2. It can be seen that both decongestants containing a quaternary ammonium compound are more effective than the third decongestant. The use of a nasal decongestant containing methylol gramicidin would appear to have a more reasonable basis in view of the *in vivo* inactivation of the tyrocidin and the toxicity and the greater hemolytic activity of the unmodified gramicidin components of tyrothricin.

Since the antibacterial properties of a product are of little value unless they remain constant under varying conditions of storage, Vonecidin was tested after exposure to aeration, to ultraviolet light, and to storage at 37° C. and at room temperature. Air was bubbled through the product for seven days or a sample was exposed directly to the light from a Westinghouse sterilamp for a similar period. Tests were carried out to determine the critical killing time as described above, using Staphylococcus aureus as the test organism. The results presented in Table 3 show that the germicidal action is not significantly changed during storage under the various conditions of exposure.

Self-Sterilizing Properties.

Gompertz and Michael (1942) have seriously incriminated the nose drop bottle as a source of contamination and spread of infections from person to person. They advocate the practice of Parkinson (1940), in which the medication is handled aseptically and does not become contaminated. This is a desirable practice in the dispensing and use of all medicinals, but the manufacture of a nasal medication with these directions is no guarantee that the preparation will be so used. There-

TABLE 3. CRITICAL KILLING TIME OF VONECIDIN AFTER VARIOUS STORAGE CONDITIONS.[1]

Storage Condition	Killing Time in Minutes — No Serum									10% Serum								
	¼	½	¾	1	1½	2	3	4	5	¼	½	¾	1	1½	2	3	4	5
No storage	+	+	+	+	+	+	—	—	—	+	+	+	+	+	+	+	—	—
14 wks. at room temp.	+	+	+	+	+	—	—	—	—	+	+	+	+	+	—	—	—	—
7 days at 37° C.	+	+	+	+	+	—	—	—	—	+	+	+	+	—	—	—	—	—
Aerated for 7 days	+	+	+	+	+	—	—	—	—	+	+	+	+	+	—	—	—	—
U-V light for 7 days	+	+	+	+	+	—	—	—	—	+	+	+	+	—	—	—	—	—

[1]Test organism, Staphylococcus aureus.

fore, to protect the user, the product should have antibacterial properties against any possible contamination. There can be no objections to such added safety provided that the product remains nontoxic.

To evaluate the self-sterilizing properties of Vonecidin, 10 ml. portions were inoculated with 0.1 ml. of a 1:1,000 broth dilution of test organism. Organisms employed were three of the more resistant, as shown in the spectrum of activity (Pseudomonas aeruginosa, Escherichia coli and Staphylococcus aureus), a less resistant organism of clinical importance (Streptococcus hemolyticus), and two common contaminants (a spore suspension of Bacillus subtilis, and a suspension of Aspergillus niger). This selection of test organisms was felt to be both representative and critical of any self-sterilizing action of the product.

Plate counts were made in triplicate after 10 minutes and again after 60 minutes, during which time the samples stood at room temperature. Suitable nutrient agar media were used for the counts.

To give some estimate of the degree of inoculation, a similar test was run, substituting sterile saline for the Vonecidin and making the viable plate counts at the 10-minute point.

Since organisms present in nasal secretions may have greater resistance to the germicidal action of the nose drop than

those in broth culture, or since the nasal secretions may lower the activity of the nose drop or add to it essential nutriment or factors necessary for the survival of the organism, actual contamination of the nose drop was attempted.

A 10 ml. portion of Vonecidin in a one-ounce dropper bottle was successively contaminated by six individuals. Each individual used a fresh sterile dropper in both nostrils and returned it to the bottle containing the nose drop. The bottle was shaken to dislodge any particles, and the nose drop was flushed in and out of the dropper several times. The dropper was then discarded, and the nose drop was contaminated by the next individual, employing a new sterile dropper. Each contamination required approximately one minute. Plate counts were run of the nose drop (0.1 ml. in triplicate), on the original uncontaminated material, at exactly 10 minutes after the first contamination, and again at the 60-minute point. As before, a control was made substituting sterile saline for the Vonecidin to give some estimate of the degree of contamination.

For this test, an infusion agar containing the neutralizing agents lecithin and Tween 80, plus added rabbit blood, was employed. The results are presented in Table 4.

TABLE 4. SELF-STERILIZING PROPERTIES OF VONECIDIN.

Test Organism	Number of Bacteria Per Ml.[1]		
	Saline	Vonecidin	
	10-Minute	10-Minute	60-Minute
Pseudomonas aeruginosa	3,660	6	3
Escherichia coli	10,220	50	23
Staphylococcus aureus	6,060	20	5
Bacillus subtilis (spores)	17,180	15,780	16,660
Aspergillus niger	340	303	20
Streptococcus hemolyticus	245	5	5
Nasal contamination	1,560	3	3

[1]Average of three plate counts.

These data show that against organisms of known resistance, Vonecidin is rapidly germicidal, effecting a marked reduction in the count (99 to 100 per cent kill) of vegetative

bacteria. There is no significant reduction in the number of viable spores of Bacillus subtilis. This determination was included to show the validity of the counting procedure. Against the contaminant mold, the action was less rapid, but definite. A similar effect was noted in the series contaminated by used droppers.

SUMMARY.

1. Vonecidin, a new decongestant containing an active nontoxic antibiotic derivative and a quaternary ammonium germicide, has been described.
2. Vonecidin has been shown to have a low surface tension, and a pH value within the normal physiologic range.
3. The antibacterial spectrum has been presented and Vonecidin has been shown to be effective against a range of organisms. Germicidal action is not significantly changed during storage under various conditions.
4. The evaluation of the self-sterilizing properties of Vonecidin showed it to be germicidal, effecting a marked reduction in bacterial numbers of known common contaminants.

REFERENCES.

ADDISON, C. C.: Surface Tension and Detergency. *Nature*, 160:467, 1947.

BUHRMESTER, C. C.: Further Studies in Hydrogen Ion Concentrations of Nasal Secretions. *Arch. Otolaryngol.*, 27:83-90, 1938.

CROWE, S. J.; FISHER, A. M.; WARD, A. T., JR., and FOLEY, M. K.: Penicillin and Tyrothricin in Otolaryngology, Based on a Bacteriological and Clinical Study of 118 Patients. *Ann. Otol., Rhinol. and Laryngol.*, 52:541-572, 1943.

DOLOWITZ, D. A.; LOCH, W. E.; HAINES, H. L.; WARD, A. T., JR., and PICKRELL, K. L.: The Prevention of Ear and Nasal Sinus Complications of the Common Cold. *Jour. A. M. A.*, 123:534-536, 1943.

DOWDESWELL, R. M.: Sinusitis and the Common Cold. *Lancet*, 2:763, 1942.

DUBOS, R. J.: Microbiology. *Ann. Rev. Biochem.*, 11:659-678, 1942.

FABRICANT, N. D.: The Local Use of Sulfonamides in Nasal and Sinus Infection: An Analytical Review. *Am. Jour. Med. Sci.*, 206:546-553, 1943.

GOMPERTZ, J. L., and MICHAEL, PAUL: Nose Drop Contamination in Dropper Bottles. *Jour. A. M. A.*, 118:1287-1288, 1942.

HEATLY, C. A.: Local Medication of the Upper Respiratory Tract. *Jour. A. M. A.*, 107:1887-1889, 1936.

HENDERSON, JOHN: The Status of Tyrothricin as an Antibiotic Agent for Topical Application. *Jour. A. Ph. A.*, 35:141-147, 1946.

JULIANELLE, L. A., and SIEGEL, MORRIS: The Epidemiology of Acute Respiratory Infections Conditioned by Sulfonamides. II. — Gross Alterations in the Nasopharyngeal Flora Associated with Treatment. *Ann. Int. Med.*, 22:10-20, 1945.

LEWIS, J. C.; DIMICK, K. P.; FUESTEL, I. C.; FENOLD, H. L.; OLCOTT, H. S., and FRAENCKEL-CONRAT, H.: Modification of Gramicidin Through Reaction with Formaldehyde. *Sci.*, 102:274-275, 1945.

PARKINSON, S. N.: Preparation of Physiologic Solution for Nasosinal Treatment. *Arch. Otolaryngol.*, 32:959-961, 1940.

PULLEN, R. L.: An Introductory Consideration of Respiratory Infections. *Med. Clin. N. Am.*, 31:1322-1343, 1947.

QUISNO, R. A., and FOTER, M. J.: Cetylpyridinium Chloride. I Germicidal Properties. *Jour. Bact.*, 52:111-117, 1946.

QUISNO, R. A.; GIBBY, I. W., and FOTER, M. J.: A Neutralizing Medium for Evaluating the Germicidal Potency of the Quaternary Ammonium Salts. *Am. Jour. Pharm.*, 118:320-323, 1946.

RUMREICH, A. S.; SHAUGHNESSY, H. J.; MULCAHY, J. V.; WILLETT, J. C.; KELLOGG, W. H., and MITCHELL, W. C.: A Nationwide Study of the Bacterial Etiology of the Pneumoniae. *Pub. Health Rep.*, 58:121-135, 1943.

TREMBLE, G. E.: The Conservative Treatment of Sinusitis in Children. *Canad. Med. Assn. Jour.*, 49:496-501, 1943.

TREMBLE, G. E.: Some Observations on Nasal Cilia. *Canad. Med. Assn. Jour.*, 56:255-259, 1947.

TURNBULL, F. M.; HAMILTON, W. F.; SIMON, E., and GEORGE, M. F., JR.: New Sulfa Compound, Desoxyephedronium Sulfathiazole, for Treatment of Sinusitis. THE LARYNGOSCOPE, 53:533-545, 1943.

WARREN, M. R.; BECKER, T. J.; MARSH, D. G., and SHELTON, R. S.: Pharmacological and Toxicological Studies on Cetylpyridinium Chloride, a New Germicide. *Jour. Pharmacol.*, 74:401-408, 1942.

WHALEN, E. J.: Sulfonamide Compounds in the Treatment of Infections of the Nasal Sinuses. *Arch. Otolaryngol.*, 40:481-486, 1944.

PENICILLIN IN THE TREATMENT OF DISEASES OF THE EAR, NOSE AND THROAT.*

VIRGIL L. PAYNE, M.D.,
Pine Bluff, Ark.

The therapy of penicillin has been the greatest addition in the last decade to our armamentarium of antibiotics and drugs for the treatment of diseases of the ear, nose and throat. In my experience, the most practical method of administration is to give 300,000 units of penicillin G sodium in a liquid oil and wax mixture intramuscularly every 12 hours.

In 1896, Gosio, while investigating spoiled maize, identified and cultured a mold called penicillium glaucum, but it remained for Sir Alexander Fleming, of London, in 1929, to identify the mold as penicillium notatum, and he called the antibacterial product elaborated by the mold penicillin. For his great discovery he was made a knight by the King of England, one of the few medical men to receive such an honor. In 1940, Florey, Chain, *et al.*, at Oxford University, and Dubos at the Rockefeller Institute contributed greatly to the research of penicillin and its present-day use and dosage.

I. — Properties.[1]

1. Penicillin is prepared commercially in the form of crystalline sodium, calcium and potassium salts, and when protected from air and moisture is stable at room temperature.

2. Penicillin is soluble in water, glucose and saline solutions to the extent of 100,000 units or more per cc.; in solution, it is very unstable at room temperature.

3. It is unstable in very dilute acids and alkalis, below a pH of 5 and above 7, and to oxidizing agents and heavy metals.

*Read at the meeting of the Southern Section, American Laryngological, Rhinological and Otological Society, Inc., Jan. 16, 1948.

Editor's Note: This ms. received in Laryngoscope Office and accepted for publication, Feb. 24, 1948.

4. It is quickly activated by the enzyme penicillinase.

5. It is specific in its action and is highly bactericidal to certain organisms in their growing phase. It is effective mostly against Gram positive organisms. Some bacteria become resistant to penicillin after small doses and some are resistant normally.

6. It is compatible with streptomycin and the sulfonamides.

7. Penicillin does not affect the hematopoietic system.

8. An advantage is its comparative safety and absence of toxicity, especially in extremely ill or debilitated patients and in the presence of liver and kidney damage.

II. — Pharmacology.

1. Dosage: A therapeutic dose of penicillin may be defined as the amount necessary to establish and maintain in the blood stream a continuous concentration sufficient to inhibit or destroy the infecting organism; a concentration of 0.02 to 2 units per cc. will suffice for most infections. The usual conventional dose ranges from 15,000 to 40,000 units intramuscularly every three hours.

2. Absorption: Penicillin is readily absorbed when given intramuscularly; however, at the end of the first hour approximately 40 to 60 per cent of the drug may be recovered in the urine. Following a single such injection of a conventional dose, a maximum blood level is reached in about 15 minutes and falls to the usual therapeutic level in about two to three hours. When given parenterally, it is rather readily absorbed from most tissues and body cavities. There is little or no absorption from the rectum, due to the presence of penicillinase; absorption is poor from the stomach and upper intestines due to hydrochloric acid.

There are a few fundamental general principles that one should follow in the use of penicillin:

1. In view of the fact that it is specific in action, the causative organism should be ascertained before chemotherapy is started. The sensitivity of the organism and its degree of

sensitivity should be determined. No doubt this is the scientific method of using penicillin, but when you are confronted with a case of severe infection where facilities for the necessary bacteriological studies are not available, what is more justifiable under such circumstances than to start immediately the use of penicillin in the hope that the invading bacteria will prove vulnerable to the antibiotic? If no beneficial effect is seen in three or four days, in the absence of laboratory data

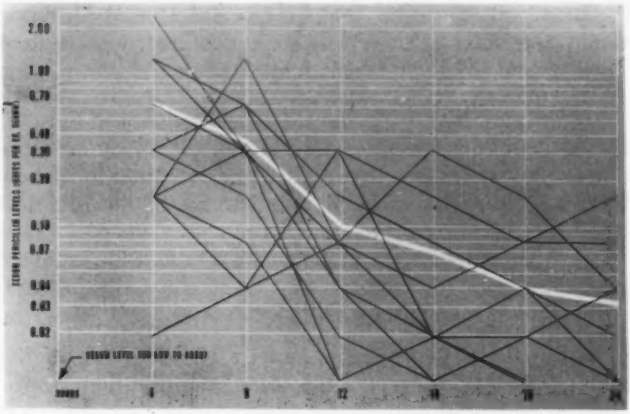

Chart 1. Serum penicillin levels in 10 different individuals, following a single 1 cc. injection **once daily** of 300,000 units Crystalline Penicillin G Sodium in Oil and Wax. The heavy line is the mean response of the group. It is apparent from the data that effective concentrations can be produced relatively quickly with this dosage, and maintained for approximately 24 hours; however, the great variations in the serum levels of the different patients emphasize the unreliability of any single figures as a guide to dosage.

Note: Although most patients show relatively high penicillin levels within 30 minutes after an injection of penicillin in oil and wax, and also show sustained or increased levels during the first four hours, the penicillin serum determinations shown in Charts 1, 2 and 3 were made only at the four-hour intervals indicated.

it is reasonable to assume, then, that it is ineffective. The patient's clinical response many times is a better guide to dosage and serum level concentration than laboratory findings.

2. In mild infections such as the common cold, where complications are said to occur at the rate of about one to 1,000

cases, a chemotherapeutic agent capable of producing more frequent and more serious complications in itself should not be given. This is especially true if one of the sulfonamides is to be administered.

3. The drug should be given every opportunity to produce a good effect. Penicillin in order to be effective must gain access to the foci which they are intended to reach through the blood

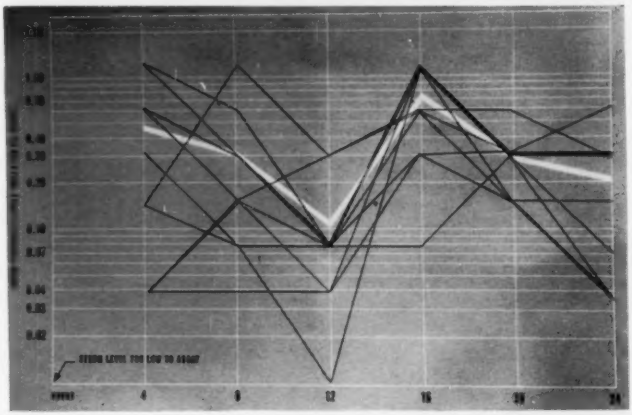

Chart 2. Serum penicillin levels in 10 different individuals, following a 1 cc. injection of 300,000 units penicillin in oil and wax every **12 hours.** As expected, the mean penicillin serum concentration curve is higher and better sustained than when injections are given once daily; however, individual curves are no less erratic than those shown in Chart 1.

stream; therefore, an adequate local circulation is a *sine qua non*[2] for the fulfillment of this purpose, as well as for that of carrying the phagocytic cells to the area. The dose should be adequate, it should be given continuously or at regular intervals throughout the 24 hours, and all primary foci should be surgically drained or exenterated.

4. The antibiotics have not replaced surgery; they have only aided it.

5. Experimental evidence has pointed to the conclusion that

the action of penicillin is not only bacteriostatic but bactericidal as well in sufficient dosage.

VARIATIONS IN PENICILLIN SERUM LEVEL TESTS.

Penicillin serum level tests, unlike many blood chemistry tests, are not always a precise measure of the amount of antibiotic in circulation.[3] The end-results are interpolations based

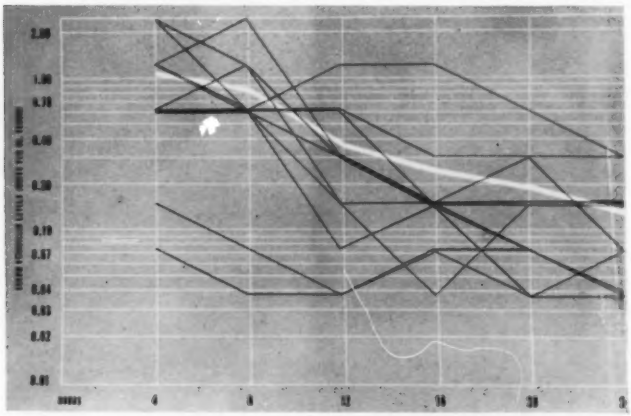

Chart 3. Serum penicillin levels in 10 different individuals, following a single injection of **600,000 units** penicillin in oil and wax in 2 cc. administered **once daily** at a single site. High initial penicillin concentrations are obtained in most patients with this dosage and these are sustained somewhat better than with a single 300,000 unit dose. Great variation in individual curves is again to be noted.

upon the ability of the serum to inhibit the growth of a standard bacterial culture *in vitro*, and are, at most, rough estimations of the quantity of penicillin in the blood at the time the sample is drawn. The results are subject to considerable error. Even the most reliable determinations of penicillin blood levels may err by 50 per cent or more; however, they have unquestionably served a useful purpose, for without them laboratory studies of the potential effectiveness of the several routes of administration of the drug could not have been utilized to support clinical study or dosage. Individuals differ

greatly in their serum level response to the same dosage or identical doses of penicillin. This is clearly seen in Charts 1, 2 and 3.

MODES OF ADMINISTRATION.

The crystalline sodium salt of penicillin G is the form most widely used today.

Orally only 20 per cent of the ingested drug is absorbed. It is necessary to give approximately five times the amount of penicillin by mouth as intramuscularly in order to obtain the same blood level. A level of approximately one unit per cc. may be obtained by the ingestion of 100,000 units every three hours. Very expensive. It should not be given just before meals, because the drug passes through the duodenum more rapidly after the ingestion of food and is thus less completely absorbed. A favorable prescription that has been clinically successful in infants with acute otitis media complicating an upper respiratory infection is prepared by suspending 400,000 units of penicillin in two ounces of amphogel and administered one teaspoonful every three hours. It has been advocated by some to prescribe penicillin tablets orally to prolong the effect, of penicillin given parenterally.

Locally: As a dusting powder, it is very irritating, and it has not been so effective as the sulfonamides. No benefit in fungus infections of external ear unless complicated by furunculosis, nor has it been very successful in chronic otitis media. As topical application in the throat or as nose drops, penicillin has not achieved much benefit; however, some authors report excellent results using the Proetz displacement method in early cases of acute upper respiratory infection and moderate nasal discharge. The technique devised by Dr. Charles Hymes[4] for the displacement of penicillin solution from the nasal chambers into the paranasal sinuses by means of self-induced intranasal negative pressure is certainly unique and worthy of trial.

Aerosal penicillin has its advantages in the treatment of infections of the respiratory tract as advocated by Davis and

Hagens.[5]. They claim a blood level of approximately 0.25 units of penicillin per cc. may be reached 30 minutes after the inhalation of 100,000 units. In children, and those who fear the needle, it has its advantages, but in serious infections other modes of administration must be relied upon. The aerosal method has been reported by Andrews and Holinger[6] as advantageous in the treatment of bronchiectasis and tracheobronchitis. The institution of early treatment, preferably the inflammatory stage of diseases of the ear, nose and throat, but especially in acute sinusitis, gives most gratifying results. The antibiotic does not diffuse rapidly through a fibrotic membrane, which characterizes chronic sinusitis.

After irrigating a sinus with sterile water, instillation of 5 cc. normal saline containing 50,000 units of penicillin decreases the necessity of frequent lavage.

Intrathecally: This is the mode usually advocated in the treatment of meningitis caused by complications of otitis media, or the epidemic type, but penicillin is retarded by the blood-brain barrier, and this method must be supplemented by injections intravenously or intramuscularly to achieve best results. High concentrations of penicillin are irritating to the meninges and should not be given intrathecally.

Subcutaneously: Absorption of subcutaneous fluids is erratic and variable. Concentrated solutions of penicillin are irritating to the skin; therefore, this method is seldom used.

Intravenously: Intravenous injection gives an immediate rise in the level of penicillin with a rapid fall, thus necessitating a continuous drip method in order to maintain a high level. An intravenous dose of 20,000 units causes an immediate rise in the penicillin level to approximately 1.6 units per cc.; however, within the first hour approximately 40 to 60 per cent of the drug may be recovered in the urine. Thus the blood level begins to fall immediately, and measurable quantities of penicillin remain in the blood for only three to four hours when given intermittently. A common usage in our specialty, after the drainage of an acute suppurative pathol-

ogy, such as acute mastoid surgery, is to give an adult intravenously 100,000 units in 1,000 cc. of 5 per cent glucose and must be given in the muscle to obtain the same serum level saline, one drop per second. This buffers the patient against an overwhelming toxemia.

Intramuscularly: The same holds true for this method as does for the intravenous use, when using aqueous or saline solutions of penicillin, only slightly higher dosages of the drug must be given in the muscle to obtain the same serum level as in the vein. Absorption is rapid, and so is excretion. The continuous method, either by vein or muscle, gives the desired

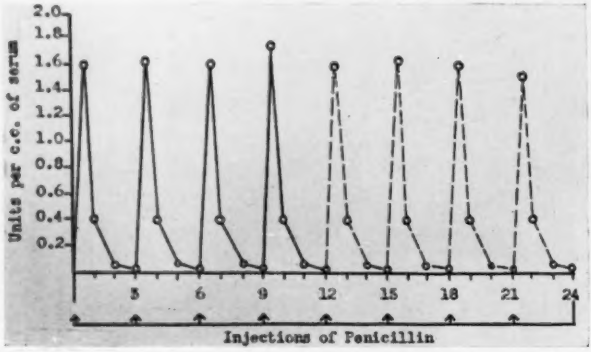

Chart 4. Blood level curve obtained by intermittent intramuscular injection of 20,000 units of penicillin given every three hours. Heavy line, 0—0, represent actual observations.

blood levels, for it is doubtful whether intermittent peaks of penicillin concentration depress bacterial growth effectively, as demonstrated by Harford and Smith,[7] shown in Chart 4. The continuous methods often show reaction at point of injection, necessitate hospitalization, constant nursing care, limited activity of patient, creates needle fear, and entails no little apparatus; so for these reasons I prefer in all office cases, and those in the hospital who are not gravely ill with an acute fulminating infection, penicillin in beeswax and oil. In allergic individuals, however, I prefer to give saline solutions. With an injection of 300,000 units of beeswax and oil intra-

muscularly, a blood level is reached of 0.625 in 30 minutes and shows sustained and increased levels during the first four hours, at which time the serum level approximates 1.25. This level gradually falls until at the end of 12 hours the concentration of penicillin is 0.312, which is sufficient to inhibit the growth of most Gram positive bacteria. The dose may be repeated at the end of 12 hours, and now even a higher serum

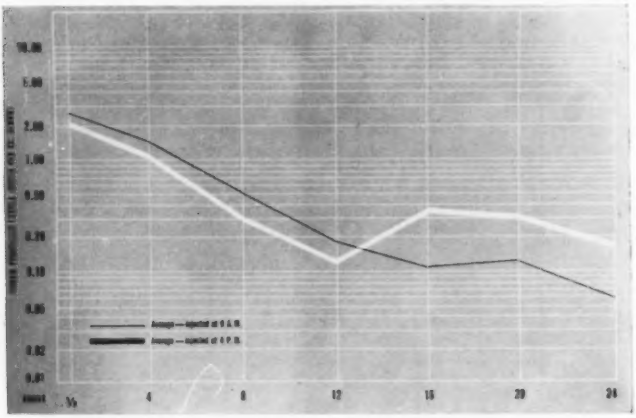

Chart 6. The mean response of two groups of patients, receiving a single 1 cc. injection **once daily** of 300,000 units Crystalline Penicillin G Sodium in Oil and Wax, one group being injected at 9 A.M. and the other group at 4 P.M. It is to be noted that the group which was injected in the late afternoon had higher and better sustained blood levels in the second twelve-hour period than did the group that was injected in the morning.

level is attained than with the first dose. High concentration of drug, ease of administration, patient usually can keep working, needled only once each 12 hours, low cost of drug, when purchased in 10 cc. vials, have led me to use this method in all cases except allergic individuals, meningitis, or patients seen late in the course of their infection, who are critically ill. In the ambulatory case, I give the beeswax and oil injection in the late afternoon so he can go home and remain quiet, for tests have shown that muscular activity tends to hasten

the absorption of the drug, as the muscles act to massage the depot of penicillin, as seen in Chart 6.

Penicillin adds nothing of benefit to the treatment of diphtheria which should always be treated with antitoxin, but

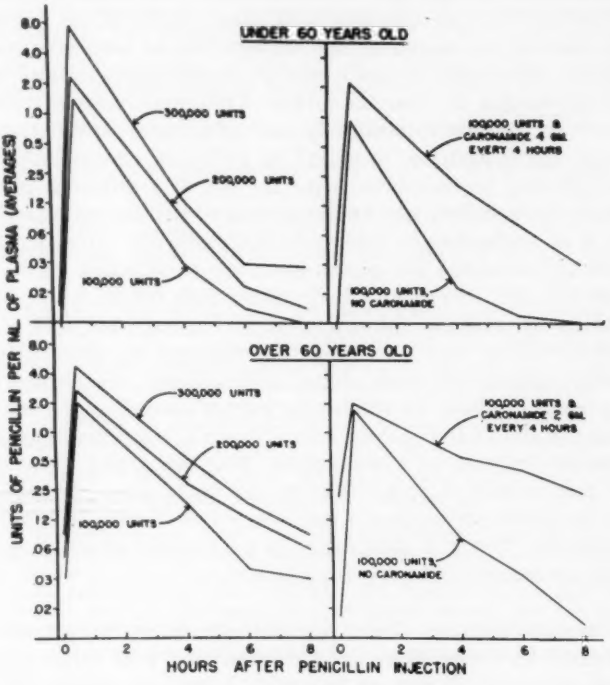
UNDER 60 YEARS OLD
OVER 60 YEARS OLD
UNITS OF PENICILLIN PER ML. OF PLASMA (AVERAGES)
300,000 UNITS
200,000 UNITS
100,000 UNITS
100,000 UNITS & CARONAMIDE 4 GM. EVERY 4 HOURS
100,000 UNITS, NO CARONAMIDE
100,000 UNITS & CARONAMIDE 2 GM. EVERY 4 HOURS
HOURS AFTER PENICILLIN INJECTION

Chart 7.

penicillin has proved to be the best treatment available for the carrier state. Place[8] states carriers are almost invariably rendered bacteria-free if given 300,000 units intramuscularly daily for one week.

Reactions may be due to impurities in the penicillin, an

ingredient of the vehicle, or sensitivity to the penicillin itself, and may appear as irritation of oral or respiratory mucosa, asthma and exfoliative dermatitis. Delayed development of reaction similar to serum sickness may occur. Kolb and Gray[9] reported peripheral neuritis as a complication of penicillin therapy, giving seven cases, all of which recovered in seven months. Allergic manifestations are usually dermal and range from an urticaria to an ulcer. Some of the patients will develop an edema of the extremities so extensive as to require immersion in solutions of magnesium sulfate, and the application of calamine lotion. Treatment is to withdraw penicillin therapy immediately and administer antihistamine drugs, pyribenzanine, benadryl or hydrelon. Sometimes the therapy may be reinstated with the use of a different preparation of penicillin, and applying cold to the site of injection, but it is preferable to substitute streptomycin. Dressler and Dwork[10] advocated for serum sickness an infusion intravenously of 1 gm. of procaine hydrochloride in 500 cc. of isotonic solution of sodium chloride (0.2 per cent) by slow drip method. Fever was a complication reported by Harford and Smith.[7] There are some drugs which delay the absorption of penicillin, either by inhibiting kidney secretion or neutralizing the Hcl of the gastric juice. These are sodium benzoate, trisodium citrate, as advocated by Broh-Kahn and Pedrick,[11] and caronamide. Caronamide, or the trade name "Staticin," may be given adults, 2 to 4 gm. every four hours, children in proportion. Chart 7 illustrates its prolonging effect of penicillin, as recommended by Singleton.[1]

Contraindications: There are virtually no contraindications to penicillin, either alone or in combination with other treatment; however, if patient has high degree of sensitivity to penicillin, administer with extreme caution or abandon this therapy entirely.

CASE REPORTS.

Some of these cases were seen in the hospital and bacteriological studies were made; others seen at the office, penicillin

in beeswax and oil was administered without laboratory studies.

Case 1: Furunculosis of the nose with suspicious cavernous sinus thromboses.

Well developed and nourished white male, age 50, en route from St. Louis to Dallas, was taken off train at our city, acutely ill. Four days previously he had pulled some hairs in the right side of his nose, which he was prone to do. The day before, he thought he had a chill. The right side of his nose, especially the tip, was red and swollen, the right ethmoidal area and upper right lid were edematous and the whole right side of his face was very painful. I saw him at the hotel, and as he would not go to the hospital no cultures were taken, but I had my nurse give him 300,000 units of penicillin in beeswax and oil every 12 hours for four doses. After the fourth dose he resumed his trip to Dallas, Tex., his nose entirely healed.

Case 2: Right quinsy in acute inflammatory stage in white female, age 24.

Aborted with three doses, 300,000 units every 12 hours; temperature shown in Chart 8.

Case 3: Acute exacerbation of chronic mastoiditis required surgery and then penicillin in beeswax and oil.

White female, age 26, married, no children, thin and had the appearance of an acutely ill patient. History negative except for discharging right ear, off and on, past four to six years. Ear had been discharging past two weeks, very painful past few days. Was treated in another city for last two weeks with local swabbing, sulfonamides, and penicillin shots. Examination revealed nose and throat negative, left ear normal. There was a large perforation of the right drum, external canal contained thick pus, and there was acute pain on pressure over the mastoid. Temperature was 102°. Patient sent to hospital for laboratory study and Roentgenograms of mastoids were made. Blood findings were those of acute infection, and X-ray report that of acute mastoiditis. She was operated upon that night, using sodium pentothal intravenously as the anesthetic. I found the usual pus, granulations, etc., in this type of mastoid. Culture revealed nonhemolytic streptococci. As soon as she reacted, penicillin in beeswax and oil was given in 300,000 unit doses every 12 hours for four doses. Her temperature came down rapidly, and on the fourth day was normal, and she left the hospital on the seventh day. She was given penicillin tablets, 50,000 units, every three hours by mouth to prolong the action of her penicillin by the previous parenteral route. She had had large amounts of penicillin before I saw her, but it did not take effect until the pathologic process was removed by surgery.

Case 4: Acute laryngotracheobronchitis requiring emergency tracheotomy.

White male, age four years, was seen by several doctors, general and otherwise, for about a week before a pediatrician saw him the day he called me. The little fellow had been treated for bronchitis, croup, asthma, diphtheria, etc., and given penicillin and the sulfonamides in large doses, but of no avail. This morning, as soon as the pediatrician saw the child, he rushed him to the hospital, calling me to meet him in the operating room to do a tracheotomy. We keep an emergency set ready at all times, so I hastened to the operating room and did an emergency tracheotomy. There was no time for passing a scope, as the child looked as though he would die, so there was nothing tranquil about the procedure. When I opened the trachea, there was an explosion of thick,

frothy pus; culture was taken and tube inserted and anchored. His color cleared, the little fellow seemed to look up at me and smiled, then closed his eyes, in what seemed to his mother to be such a quiet, restful sleep, and to me also. He was given continuous penicillin intravenously for several days, as well as inhalations. The laboratory was never able to grow a culture from the pus taken from the trachea, which probably was a result of all the drugs he had previously. This was another case of surgical drainage before penicillin was effective. The tube was removed in two weeks, and the youngster left the hospital in good shape.

Case 5: Deep neck abscess — surgery and penicillin.

White male, age 18. Three weeks previously had swallowed a piece of toothpick. Seemed to lodge in left side of throat, but he could never get it out. Neck began to swell on left, became painful, and he could hardly open his mouth; dysphagia also. Had much penicillin, sulfa drugs, etc., but grew worse. Under local anesthesia, neck was drained. Thick, foul-smelling pus returned. Cultured B. coli. Catheter drain sutured in wound. Penicillin in beeswax and oil was given. Uneventful recovery.

Case 6: Gas gangrene in fractured face and left frontal sinus — loss of left eye.

Colored male, age 26, crushed when house was blown away during cyclone. Left side of head fractured, through maxilla, orbit, eyeball perforated, left frontal sinus fractured, and face badly lacerated. Within 12 hours tissues had ballooned up. Laceration of thigh also showed crepitation of skin. Organisms predominantly present were B. Welchii and anerobic streptococci. No surgery performed. Wounds only treated locally. Left eye ordinarily should have been enucleated. Antitoxin and large doses of penicillin, 100,000 units, given hourly for about one week, then every two to three hours for another week. Eventually he recovered and repair was done to his face. There were several other cases of gangrene in the hospital at the same time, injured in the tornado, who recovered. One white female, age 32, from whom large portions of flesh were sloughed from her buttocks and thighs. X-rays of these cases were interesting, and when the skin was punctured it sounded like sticking a needle in a bicycle tire. We believed penicillin aided these cases greatly. Dr. J. S. Wood, divisional director of the National Red Cross from St. Louis, who had been at the scene of the Texas City disaster only a short time before, was sent to Pine Bluff, and he said in Texas they had many cases of gas gangrene, and the doctors there believed their good results were due to the large, frequent doses of penicillin given. Herrell[12] states, while penicillin may definitely inhibit the growth of the organisms associated with gas gangrene, the neutralizing effect of antitoxin is essential.

CONCLUSIONS.

1. Penicillin specific in action. Practically nontoxic.

2. Organism may be resistant or acquire resistance to the drug, and individuals may be sensitive to it.

3. Success due to high sustained blood levels.

4. I believe penicillin beeswax and oil given intramuscularly every 12 hours is the most practical method of administration. The new preparation needs no heating and liquefies easily.

5. The drug often causes masking of symptoms.

6. Consensus of opinion, penicillin achieves best results in acute inflammatory stage, especially of accessory nasal sinuses.

7. The antibiotic must reach the organisms to be effective, and this is best accomplished through the blood stream.

8. Penicillin has not replaced surgery.

I express my appreciation to Dr. H. Sidney Newcomer for the valuable assistance he rendered in this work, to his company, E. R. Squibb and Sons, who furnished the penicillin used in my cases, and to the Squibb district representatives, Mr. Dewey G. Nicks and Mr. W. P. Grinstead, of Little Rock, Ark., whose cooperation aided me greatly.

REFERENCES.

1. Singleton, J. Dudley: Material taken from his course given at the American Academy of Ophthalmology and Otolaryngology, October, 1947, at Chicago.

2. McMahon, B. J.: Influence of Sulfonamides and Antibiotics on the Future of Otolaryngology. *Ann. Otol., Rhinol. and Laryngol.*, 55:298-305, June, 1946.

3. Squibb, E. R., and Sons: Research Dept., Penicillin Blood Levels an Ever-Changing Picture.

4. Hymes, Charles: A Simplified Technique for the Introduction of Penicillin into the Paranasal Sinuses. *Tr. Am. Acad. Ophthol. and Laryngol.*, pp. 173-178, 1947.

5. Hagens, E. W.: Inhalation Method for Penicillin Therapy. *Arch. Otolaryngol.*, 41:333-336, May, 1946.

6. Andrews, Albert H., Jr., and Holinger, Paul H.: Penicillin Therapy in the Trachea and Bronchi. *Ann. Otol., Rhinol. and Laryngol.*, 55: 617-628, Sept., 1946.

7. Harford, Carl G., and Smith, Ralph O.: The Administration of Penicillin by Continuous Intramuscular Drip. *Jour. Lab. and Clin. Med.*, 30:6:502-509, June, 1945.

8. Place, Edwin H.: Present Status of Diphtheria. *Ann. Otol., Rhinol. and Laryngol.*, 56:347-351, June, 1947.

9. Kolb, L. C., and Gray, S. J.: Peripheral Neuritis as a Complication of Penicillin Therapy (with Recovery). *Jour. A. M. A.*, 132:323, Oct. 12, 1946.

10. Dressler, S., and Dwork, R. E.: Reactions to Penicillin: Procaine Hydrochloride Intravenously in the Treatment of Reactions Similar to Serum Sickness. *Jour. A. M. A.*, 133:849, Mar. 22, 1947.

11. Broh-Kahn, R. H., and Pedrick, R. F.: Some Factors That Modify the Effect of Trisodium Citrate on the Absorption of Oral Penicillin. *Am. Jour. Med Sci.*, 212-691, Dec., 1946.

12. Herrell, Wallace E.; Nichols, Donald R., and Heilman, Dorothy: Mayo Clinic. *Jour. A. M. A.*, 125:1003-1010, Aug. 12, 1944.

THE RATIONAL BASIS FOR THE USE OF VITAMINS IN THERAPEUTICS.*

AGNES FAY MORGAN, M.D. (by invitation),

Berkeley, Calif.

The aura of mystery which at first surrounded the identity and function of the vitamins has largely been dispelled in recent years. The rapid isolation, chemical identification and synthesis of nearly all the vitamins began in 1932 with the proof of the structure of ascorbic acid, was followed in 1933 by the discovery of the nature of riboflavin, in 1936 by the synthesis of thiamine and tocopherol, in 1938 by the proof of structure of pyridoxine, in 1937 by the discovery of the vitamin character of nicotinic acid, in 1940 by the synthesis of pantothenic acid. Meanwhile, other substances of well known and relatively simple chemical composition were found to have definite vitamin-like functions. Some of these are para-aminobenzoic acid, inositol and choline. In 1946, the structure of "folic acid" or pteroyl-glutamic acid was determined and the substance synthesized. The composition of vitamins A, D and K is now likewise well known and all have now been synthesized. The magic and mystery of what they are has been dispelled, but the full story of what they do and especially how is not yet known. Until the mechanism of the physiological action of the vitamins has been uncovered, the rational use of vitamins as prophylactic and curative agents in medical practice cannot be effected.

In the earlier experimental studies the obvious effects of single vitamin deficiencies were recorded. These were largely observations on growth of young animals, skin and eye lesions, development of infections, changes in blood and tissue composition and microscopic anatomy. The too literal interpretation of these effects led to the characterization of certain

*Read at the meeting of the Western Section, American Laryngological, Rhinological and Otological Society, Inc., Jan. 31, 1948.

Editor's Note: This ms. received in Laryngoscope Office and accepted for publication, Feb. 24, 1948.

vitamins as anti-infective, antidermatitic, anticanitic, antisterility, etc. Another error often made was the assumption that deficiency symptoms obtained in one species will appear in all others, including the human; but riboflavin deficiency, for example, which produces skin eruptions, cataracts and loss of hair in rats, has none of these effects in dogs. Pyridoxine deficiency quickly causes convulsions and severe hypochromic anemia in dogs and swine, but these changes are difficult if not impossible to produce in rats or mice.

It is not reasonable to suppose that the fundamental derangement of nutrition due to a vitamin deficiency is different in different species. If this were so, we should have to postulate different functions implemented by the same vitamin in the species compared. Instead, modern investigations with tissue slices, cell-free tissue extracts and micro-organisms indicate the involvement of several of the vitamins in one or more enzym systems. If a vitamin is the prosthetic molecule of a coenxy-enzym combination affecting the respiration of a wide variety of tissues, diverse abnormal conditions might be expected to result from any deficiency in the vitamin.

The enzyms themselves have only recently emerged from mystic obscurity as to composition and mode of action. They differ from vitamins and the essential amino acids in that they are synthesized in their entirety in the animal body, presumably from the amino acids provided by the diet. Apparently a breakdown of the enzym systems due to dietary reasons is likely to be due not to lack of enzyms themselves but rather to lack one or more of the vitamins essential to the coenzym complex. The result of enzym failure may be widespread if essential oxidations are involved. The structural damage and functional failures of some vitamin deficiencies may well be secondary results of these biochemical lesions. The nature of the failure noted is doubtless influenced by auxiliary and unbalanced reactions promoted by those enzym systems which are still operating normally. There may also be present in the deficient diet naturally occurring inhibitors or antivitamins, unable to serve as substitutes for the missing vitamin, but sufficiently similar in structure to take its place in the enzym system, thus blocking its operation. The prevalence of

pellagra, for example, in corn-eating populations has been ascribed by Woolley,[1] not so much to the lack of nicotinic acid in the corn as to the presence of antinicotinic acid compound.

Most of the B-complex vitamins have been found to function in coenzyms. The first instance noted in 1931 by Gravilescu and Peters[2] was in relation to the lowered oxygen uptake of thiamine-deficient pigeon brain, which was quickly increased when thiamine was added. Pyruvate accumulated in the absence of thiamine but was removed in its presence. Pyruvate is an important metabolite of carbohydrate which is decarboxylated by the long recognized enzym carboxylase but only when cocarboxylase is present. The latter was shown in 1932 to be thiamine pyrophosphate. This substance serves as prosthetic grouping for other decarboxylases, also, *e.g.*, α ketoglutarate and α ketobutyrate.

The various manifestations of thiamine deficiency must be largely, if not wholly, due to functional failures in carbohydrate-using organs and tissues, followed in some cases by consequent structural changes. The lesions of the nervous system seen in Wernicke's syndrome are identical with those produced in certain experimental thiamine deficiencies and may in fact be caused by low thiamine intake, particularly evident in alcoholics. "Beriberi heart," involving right-sided enlargement and decreased circulation time, is due to thiamine deficiency and is also found in alcoholism. The heart, like the brain, is a carbohydrate-using organ which may well deteriorate under the anoxic and undernourished conditions of low thiamine intake.

Every brain, heart and nerve lesion simulating those known to be relieved by thiamine may not be ascribed to the deficiency. Other quite different conditions involving no failure of decarboxylation can and do produce similar syndromes. In these cases no alleviation follows the most lavish use of thiamine by every route.[3] There is one possibility, however, that may be worth noting: a long-continued subacute deficiency may result in irreversible tissue changes, even though the biochemical lesion may have been largely corrected.

Riboflavin was first noted as a constituent of the "yellow

enzym" prepared by Warburg and Christian in 1932[4] from yeast. Its vitamin character was established only after its coenzym function was known. Riboflavin combined with phosphoric acid and a protein acts as mediator in at least five oxidoreduction reactions involving amino acids, xanthine, triphosphopyridine nucleotide (TPN) and certain carbohydrate metabolites. Obviously tissues in which respiration takes place must be adequately supplied with these flavoproteins, particularly those tissues such as the epidermis and cornea which are poorly vascularized, since the flavoproteins act as oxygen carriers or hydrogen receptors much as hemoglobin does. The symptoms of riboflavin deficiency may be expected to be diverse and often obscure. The accepted picture of cheilosis, hyperemia of buccal mucosa and corneal vascularization depicts the external and perhaps least important of these changes. There is some evidence that the adrenal cortex may be progressively exhausted in riboflavin deficiency, since under anoxia, deficient rats are unable to increase their carbohydrate content and this disability may be removed either by riboflavin or adrenal cortical extract injections.[5] Hemorrhages were found in the adrenals of dogs which died suddenly of the deficiency. These animals had extremely low blood sugar and liver glycogen. Disturbances of water metabolism in riboflavin-deficient rats[6] have been reported and these were curable either by the vitamin or adrenal cortical hormone. These adrenal changes may also involve hypophyseal and other endocrine changes, and may in fact be only one manifestation of the general oxidative failure.

Nicotinic acid (or nicotinamide) is also part of the oxidase system, since nicotinamide is present in coenzyms I and II or diphosphopyridine nucleotide (DPN) and triphosphopyridine nucleotide (TPN). The existence of these coenzyms was proved chiefly by von Euler[7] and by Warburg and Christian,[8] in the 1930's, and the presence of nicotinamide in them may have suggested in 1937 its use as a cure for black tongue in dogs.[9]

No less than 35 carbohydrate metabolic reactions have been shown to depend upon the presence of these coenzyms, but

some of these at the same time require also the presence of riboflavin-containing flavoproteins.

The multiple nature of the deficiency disease, pellagra, was recognized soon after nicotinic acid began to be used clinically. Thiamine, riboflavin and possibly protein deficiencies occur in most pellagrins and nicotinic acid therapy alone is only palliative. The superficial symptoms of nicotinic acid deficiency, dermatitis and diarrhea, represent the visible result of far-reaching metabolic failure in many tissues and glands. The neuropathy early causes personality and mental changes and eventually may produce the dementia of pellagra. In our experiments with pure nicotinic acid deficiency in dogs, we have noted the damage to the liver as the terminating factor. Apparently when the yellow, fatty and sometimes cirrhotic degeneration proceeds beyond a certain point the condition is irreversible. In a recent series of reports from South Africa[10] the high incidence of liver disease and of liver cancer among the corn-eating native population was stressed. Seventy per cent of the adult population dying in accidents were said to have liver pathology, 9.4 per cent having cirrhosis. The organs or tissues most seriously affected by a coenzym deficiency may well be those in which the oxidase systems employing them are normally most active. The liver is particularly rich in nicotinamide and is the site of very active metabolism.

Pantothenic acid has recently been shown to be present in a coenzym active in acetylation,[11] and may well be the activator required for production of acetyl choline in cell-free brain extracts.[12] This vitamin occurs naturally almost entirely in bound form, associated with protein and widely distributed as the coenzym in metabolically active tissues.

The external signs of pantothenic acid deficiency are graying of the hair, skin lesions, loss of elasticity of skin, sometimes coma or convulsions, low gastric acidity and motility and intestinal ulceration.

That the adrenal glands are progressively affected by the deficiency was demonstrated[13] in 1939. This results in disturbances of carbohydrate and water metabolism. We have

seen striking similarities between the terminal stages of riboflavin and pantothenic acid deficiencies in dogs, in both of which low blood sugar, coma, convulsions and adrenal hemorrhages are found. Parallel or coordinated functions of the acetylating coenzym containing pantothenic acid and the flavoproteins containing riboflavin may explain this resemblance.

Pyridoxine was from the first associated with amino acid metabolism, since the abnormal excretion of tryptophane metabolic end-products was noted in pyridoxine-deficient animals.[14] In experiments with micro-organisms and yeast, derivatives of pyridoxine, pyridoxal and pyridoxamine were shown[15] to function as coenzyms for transamination and decarboxylation of certain amino acids. This was shown also by decrease of transaminase content of tissues of pyridoxine-deficient animals. The great variety of pyridoxine deficiency symptoms in different species may be due to differences in rate and character of amino acid metabolism in various organs and tissue. In the dog and the pig the first failure is in hemoglobin production, but in the rat and the mouse this is late in developing. The convulsions exhibited by the dog and the pig may be related to demyelinization of peripheral nerves and degeneration of the axial cylinder which has been seen in swine.

If the pyridoxine-containing coenzym is necessary for transamination and decarboxylation of one or several amino acids its absence may well be expected to bring about numerous and diverse failures of function and pathology of tissues.

Pteroylglutamic acid, formerly called folic acid, and para-aminobenzoic acid may be considered together since it is likely that the latter is required chiefly as a constituent of the former. Failure of hematopoieses with hypoplasia of bone marrow characterizes the folic acid deficiency state. One investigator[16] from experiments with hyperchromic anemic dogs and pernicious anemia patients has concluded that folic acid may be required for cholinesterase activity and for maintenance of normal serum acetylcholine levels. When treated with liver extract or with folic acid, the serum acetylcholine

levels fell in dogs rendered anemic with acetylcholine and red blood cell counts rose. This may be an indication of another important enxym-vitamin relationship.

Biotin deficiency is manifested in rats by extensive and early alopecia and dermatitis. Biotin has recently been shown to be active in promoting the transamination of oxalacetate to aspartic acid and the fixation of carbon dioxide by which pyruvic acid is converted to oxalacetate.[17] Biotin is also needed for the decarboxylation of oxalacetate.[18] These experiments were carried out chiefly with bacterial media. In confirmation, the livers of biotin-deficient turkeys have been found to be low in the enzym causing decarboxylation of oxalacetate.[19]

Definite coenzym function has thus been ascribed to thiamine, riboflavin, nicotinamide, pantothenic acid and pyridoxine, with some evidence also in the case of pteroylglutamic acid and biotin. No such convincing proof is available for such function in the cases of ascorbic acid, vitamin A, vitamin D, the tocopherols, vitamin K or any of the less definitely established vitamin-like substances such as inositol, choline, vitamin P and numerous others.

In the effort at establishment of a general cellular function for the vitamins, three steps have usually been taken, and all of them are necessary for final proof. *1.* The *in vitro* proof of the presence of the vitamin in the enzym system operating in tissue slices or extracts, bacterial media or other preparations; *2.* the demonstration of lowered concentration of the coenzym containing the vitamin in the organs or tissues of vitamin-deficient animals; *3.* the restoration of function in both *in vitro* and *in vivo* experiments by addition of the missing vitamin, or in appropriate cases, of the coenzym. In most of the vitamins listed as functioning as coenzym, all three of these proofs have been adduced.

It is necessary now to consider how these findings may be utilized in rational vitamin therapy. The old criteria for proof of specificity of treatment hold here. The disease suspected must be shown to be present, the treatment must be uncom-

plicated by collateral palliatives and the cure must be complete and permanent. Vitamin deficiencies may be detected as suggested by Jones[20] through diet histories, laboratory tests and therapeutic trial. Of these, only the laboratory tests can be said to provide reliable diagnostic aid, although clinical improvement following dosage is indicative at least of some previous deficiency.

The diet history is sometimes helpful but is more often unreliable and may be misleading. It is possible that long past, childhood or even prenatal, nutritional failures may have established irreversible tissue changes which the later rational diet cannot reveal or remedy. Conversely, a poor diet only recently practiced may obscure the real condition. The technique of obtaining reliable diet histories is not an easy one to acquire and the elaborate paper analysis of qualitative or only roughly quantitative diets is usually not enlightening. Large differences in composition of foods, particularly as to vitamin content, may result from methods of processing, storage and especially cooking. Most of the standard tables of composition of food contain values only for raw foods and if these are modified for processing and cooking, the results must be used with recognition of the wide variations involved. On the whole, the diet history must be judged an adjunct to diagnosis, rather than a reliable guide.

Therapeutic doses of vitamins seldom involve risk, although clinical as well as experimental experience has indicated the possibility of precipitation of one or more latent deficiencies by the removal of the predominant deficiency. Thus pellagrins treated with nicotinic amide[21] were found to develop previously hidden signs of thiamine or riboflavin deficiencies. In our early experiments with nicotinic acid and filtrate factor-deficient dogs,[22] we noted earlier and more severe collapse in the animals subjected to the single than to the double deficiency. In some cases, however, a double deficiency, as, for example, that of riboflavin and pantothenic acid, produced more severe pathology than either deficiency alone. Apparently in the latter double deficiency the enzym systems affected may be interrelated and interdependent, rather than comple-

mentary. In both cases the adrenal glands appear to be the final target. We have also seen notable alleviation of the pathology resulting from hypervitaminosis D in animals receiving accompanying large doses of vitamin A.[23] Milhorat and Bartels[24] observed improvement in the use of tocopherols in muscle dystrophy when inositol was injected also, and Wright and Welch[25] claim that biotin and folic acid affect the utilization of pantothenic acid by succinyl sulfathiazole-treated rats. In some cases these inhibiting or auxiliary actions may be ascribed to effects upon intestinal bacterial activity or absorption, but in others there is reason to suspect that they may reflect diversion of the metabolic balance.

Since human dietary deficiency is nearly always multiple, the best choice of vitamin medication is often difficult. Is it enough to prescribe a generous mixture of the six vitamins for which adequate daily allowances have been set up tentatively, or should all others known to be required by other species and perhaps qualitatively by the human species be included also? No one would be rash enough to try to make a definitive list at this time of vitamin needs, particularly without reference to the composition of the diet. The need for certain vitamins is modified by the amount and kind of protein, fat and carbohydrate and of certain mineral constituents of the diet, due to both digestive and metabolic factors. A diet rich in calcium and phosphorus, for instance, greatly enhances the danger of hypervitaminosis D and one poor in tryptophane, such as the corn diet, the danger of nicotinamide deficiency. In this connection it has occurred to me that the bony regrowth following the fenestration operation might be influenced by dietary calcium and vitamin D and sun exposure, and that vitamin A might have an arresting effect on this influence.

That a single vitamin or any arbitrary mixture of vitamins can be safely or effectively used in diverse conditions seems at this time unlikely. The diagnosis by therapeutic use of vitamins rests upon chance or upon persistent, cautious, long-continued observation, including meticulous control of the patient's diet.

There remain the laboratory tests which are now being rapidly refined and calibrated. Nutritional status studies, although as yet only in their beginning, give promise of value to the internist. The blood examinations offer already reliable and rapid procedures for ascorbic acid, vitamin A and carotene, serum protein, calcium, inorganic phosphate, phosphatase, hemoglobin, cells counts, prothrombin, pyruvate and lactate. These present a picture of the status of the patient with regard to ascorbic acid, vitamin A, vitamin D, protein, calcium, iron, folic acid, vitamin K and thiamine. Roentgenograms of bones and heart give further information, biomicroscopic study of the eye, tongue and gums, and the usual physical examination for condition of external tissues may yield something of value to the experienced examiner. The saturation or loading tests involve determination of urinary excretion of ascorbic acid, thiamine, riboflavin or other water-soluble vitamin following the administration of a massive dose. The speed and completeness of excretion of the excess has been found to be correlated with the patient's status with reference to the vitamin.

Additional blood analyses are desirable, for example, for pantothenic acid, riboflavin and cholesterol. Reliable methods and adequate establishment of normal ranges are not yet available, however, for all the blood constituents of interest to the diagnostician.

The quick and easy measurement of nutritional status by use of standardized push button apparatus is not yet in sight. The dark adaptation of the eye as a measure of vitamin A status, for example, for a time gave promise of this desirable efficiency, but this has now been largely discarded because of the discrepancies between its findings and those of blood analysis and clinical observations.

In spite of the expense involved in the blood, urine and physical examinations necessary to determine nutritional status, a rational basis for the prescription of vitamins and of special diets cannot be established in any other way. The clinician who assumes that no nutritional fault exists unless the last violent superficial signs of beriberi, pellagra or scurvy

are manifested is running the risk of missing the predominant clues. Where no infection can be found to explain the patient's condition, the body cells themselves must be accused of dereliction and this dereliction may reasonably be thought to result from irregularity of the active chemical processes kept going through proper nutrition. The best diet may be consumed and yet these failures result if poor digestion and absorption, increased requirements or other conditioning factors supervene; or the effects of a poor diet in an earlier period may have culminated in the breakdown. Examples of diseases which may be subject to this interpretation are arthritis, hypertension, Ménière's, cardiac failure, nephritis, arterial disease and numerous others, perhaps including cancer. Earlier minor episodes may point the way to these catastrophies so that the nutritional errors may be detected before the biochemical lesions have produced irreversible tissue changes. The medical adviser who sees his patient often and long before that last mortal inch which is usually his only domain may serve the public health by collecting data on nutritional status. The special diets which are in the armamentarium of every internist might be amended and strengthened if these tests were made before and at intervals after the diets are ordered. The pet vitamin prescriptions that are so often advised likewise might cease to be the gunshots in the dark that they now so often are if similar laboratory controls were instituted.

In order to implement a program of this kind, consulting laboratories and central hospital services are needed. Vitamin analysis is now nearly as quick and at least as accurate as most of the roentgenological, bacteriological, serological and other routine diagnostic procedures considered indispensable to good clinics and hospitals. Institutions such as state hospitals, homes for the aged, and schools are in a particularly stategic position to make important contributions to the etiology of degenerative diseases by mass nutritional status studies.

It must not be forgotten that nutritional excesses as well as deficiencies are likely to cause disturbance of both structure

and function. There are indications that unbalanced excesses of calories, amino acids, fats, vitamins and other nutrients are involved in some of the degenerative diseases.

SUMMARY.

The mechanism of the action of vitamins is now rapidly being uncovered. In a number of cases, particuraly of vitamins of the B-complex, this has been shown to be through the presence of the vitamin in a coenzym necessary for the functioning of the enzym systems which control cellular metabolism. The manifestations of vitamin deficiency in these cases may, therefore, be widespread, variable, different in various species and progressive in character. Tissues and organs may undergo pathology as a result of the biochemical lesion and these changes may eventually become irreversible.

The detection of nutritional inadequacies is usually effected by study of diet histories, use of therapeutic doses of vitamins or other nutrients or by laboratory tests.

The diet history is at best only suggestive and is often useless or misleading. The therapeutic dose method of diagnosis is complicated by the multiple and intricate interrelationship of the metabolism, which makes difficult the choice of a safe and effective prescription.

Laboratory tests for nutritional status are now being advanced to reliable and relatively rapid aids for diagnosis. Blood microanalysis for vitamin and other constituents, urinary loading or saturation tests, microscopic and biomicroscopic examination of certain tissues, Roentgenograms of bones and heart, and other procedures are included among these methods.

Early and regular application of these tests to all patients and others who can be reached may assist in uncovering the biochemical lesions of dietary deficiency which may precede the development of the baffling pathological symptoms, some apparently reversible, which are so familiar to every clinician.

All diseases not due to micro-organisms are surely not

attributable to nutritional failures or excesses, but unless a sound program of laboratory routine designed to detect such failures or excesses is put into operation the prescription of vitamins and special diets may continue to be controversial and the uncovering of the true causes of these diseases will be delayed.

BIBLIOGRAPHY.

1. Woolley, D. W.: *Jour. Biol. Chem.*, 157:455, 1945.
2. Gravilescu, N., and Peters, R. A.: *Biochem. Jour.*, 25:1397, 1931.
3. Blankenhorn, M. A.: *Ann. Int. Med.*, 23:398, 1945.
4. Warburg, O., and Christian, W.: *Naturwiss*, 20:688-980, 1932.
5. Wickson, M. E., and Morgan, A. F.: *Jour. Biol. Chem.*, 162:209, 1946. Morgan, A. F.; Groody, M., and Axelrod, H. E.: *Fed. Proc.*, 6:415, 1947.
6. Gaunt, R.; Liling, M., and Mushett, C. W.: *Endocrinal.*, 38:127, 1946.
7. Euler, H.; Albers, H., and Schlenk, F.: *Ztschr., Physiol. Chem.*, 237, 1, 1935.
8. Warburg, O.; Christian, W., and Griese, A.: *Biochem. Ztschr.*, 279:143, 282:157, 1935.
9. Elvehjem, C. A.; Madden, R. J.; Strong, F. M., and Woolley, D. W.: *Jour. Am. Chem. Soc.*, 59:1767, 1937.
10. Gillman, J., and Gillman, T.: *Nut. Rev.*, 5:353, 1947.
11. Lipmann, F., and Kaplan, W. O.: *Jour. Biol. Chem.*, 162:743, 1946; 167:869, 1947.
12. Nachmanson, D., and Berman, M.: *Jour. Biol. Chem.*, 165:551, 1946.
13. Morgan, A. F., and Simms, H. D.: *Sci.*, 89:565, 1939.
14. Lepkovsky, S.; Roboz, E., and Haagen-Smit, A. J.: *Jour. Biol. Chem.*, 149:195, 1943.
15. Gunsaulus, I. C.; Bellamy, W. D., and Umbreit, W. W.: *Jour. Biol. Chem.*, 155:685, 1944.
16. Davis, J. E.: *Sci.*, 104:37:605, 1946.
17. Lardy, H. A.; Potter, R. L., and Elvehjem, C. A.: *Jour. Biol. Chem.*, 169:451, 1947.
18. Lichstein, H. C., and Umbreit, W. W.: *Jour. Biol. Chem.*, 170:329, 1947.
19. Ochoa, *S., et al.*: *Jour. Biol. Chem.*, 170:413, 1947.
20. Jones, I. H.: The Laryngoscope, 51:609, 1941.
21. Spies, T. D.; Vilter, R. W., and Ashe, W. F.: *Jour. A. M. A.*, 113: 931, 1939.
22. Morgan, A. F.: *Sci.*, 93:261, 1941.
23. Hendricks, J. B.,; Morgan, A. F., and Freytag, R. M.: *Am. Jour. Physiol.*, 149:319, 1947.
24. Milhorat, A. T., and Bartels, W. E.: *Sci.*, 101:93, 1945.
25. Wright, L. D., and Welch, A. D.: *Jour. Nutrition*, 27:55, 1944.

INFECTIONS OF THE EPIGLOTTIS WITH OBSTRUCTIVE DYSPNEA. (TWO CASE REPORTS.)*†‡

BERNARD FRIEDSON, M.D., and DAVID H. JONES, M.D.,
New York, N. Y.

The following is a presentation of two case reports of infections of the epiglottis with obstructive dyspnea necessitating tracheotomy.

Case 1: History: The patient is a 29-year-old white male who was admitted to the hospital at about 2:30 A. M., March 13, 1947, in acute respiratory distress.

He states that upon awakening at the usual time the morning of March 12, he noticed soreness in the throat which was worse on swallowing. During the day, he was able to follow his usual occupation of bookseller, and retired at the usual time that evening. At about 11:00 P. M. he was awakened from his sleep by severe shaking chills which lasted several minutes. Shortly after the chills had subsided, the patient noticed that he was short of breath. No history of fever was obtained.

The family physician was summoned and after superficial examination he recommended warm salt water gargles. An ambulance was also called and the interne repeated the advice of the family physician; however, the patient found that it was becoming increasingly difficult to breathe, and came to the Veterans' Hospital by taxi.

Physical: On arrival at the hospital, the patient presented the classical picture of acute laryngeal obstruction. There was a crowing sound on both inspiration and expiration. He was anxious and excited and could not find a comfortable position. Cyanosis, dyspnea, orthopnea, as well as suprasternal and infrasternal retraction on inspiration were present.

Indirect laryngoscopy revealed that the epiglottis was enlarged very markedly, dull and dark red in color. There was marked edema and redness of both aryepiglottic folds and both arytenoids. No airways could be visualized.

The temperature was 102.8° by rectum. Pulse 100. Respirations 32 per minute and labored. The skin was warm and dry. The ears and nose appeared normal. There was slight redness of the throat. There was no enlargement of the lymph nodes of the neck.

The patient was taken to the operating room and immediate tracheot-

---

*Read before the Section on Otolaryngology, New York Academy of Medicine, New York, N. Y., May 19, 1948.

†From the Department of Otolaryngology, Veterans Administration Hospital, New York, N. Y. Dr. David H. Jones, Consultant.

‡Published with the permission of the Medical Director, Branch Office No. 2, Department of Medicine and Surgery, Veterans' Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

Editor's Note: This ms. received in Laryngoscope Office and accepted for publication, June 16, 1948.

omy was performed. There was instantaneous relief of the respiratory distress upon insertion of the tracheotomy tube.

Laboratory Findings: Blood count: R. B. C., 3.7 million. W. B. C., 20,000. Differential: 83 neutrophiles, seven lymphocytes, 10 monocytes. Urinalysis negative.

Course: The patient was placed on a course of penicillin, 50,000 units intramuscularly every three hours. Intravenous fluids as well as the usual tracheotomy care were given.

On the day after tracheotomy, the temperature dropped to the maximum of 100.6°. He was still unable to swallow even fluids because of the pain on swallowing, and was maintained on intravenous fluids. Clinically, he did not appear to be quite as acutely ill as previously. Re-examination of the larynx by the indirect method revealed the presence of two white pin points on the left half of the free border of the epiglottis. Otherwise, there was no change in the appearance of the larynx.

Under direct laryngoscopy, an incision was made into the epiglottis in the region of the white spots. About 5 cc. of thin, yellow purulent matter were removed by suction. The organism was reported later as being nonhemolytic streptococci. Hot saline pharyngeal irrigations were started every four hours after the incision into the epiglottis.

The day after the incision, the patient felt much better and began to take fluids by mouth. The temperature dropped to 99.8° maximum. Slight emphysema of the neck and chest was noted.

There was gradual decrease in the size and redness of the epiglottis. Pus continued to drain from the epiglottic incision. There was only a slight thickening of the epiglottis noted on the fourth day after incision and decannulation was started.

The tracheotomy tube was removed completely on the seventh day after incision and the wound closed. Penicillin was discontinued at this time.

Examination of the larynx on the thirteenth day after incision showed that the epiglottis was still somewhat reddened and edematous.

The appearance of the larynx being normal, the patient was discharged 17 days after incision. Three million three hundred thousand units of penicillin were administered intramuscularly in all, over a period of eight days.

Case 2: History: The patient is a 23-year-old white male who was admitted Jan. 2, 1948, with a history of pain on swallowing, which began two days prior to admission and which gradually became worse. On the day prior to admission, he saw his family physician nad received 450,000 units of penicillin in oil into the gluteal region. There was no improvement in 24 hours, so the family physician recommended hospitalization.

Physical Examination: Physical examination at the time of admission revealed a well developed and well nourished white male who appeared acutely ill, but in no acute distress. Temperature 100.4°. Pulse 84. Respirations 20. The throat was reddened and injected. Indirect examination of the larynx revealed that there was pooling of saliva in both pyriform fossae. The epiglottis was somewhat reddened and edematous Both arytenoids and both aryepiglottic folds were somewhat pale, but markedly edematous. The edema extended downward mainly on the right side of the larynx to include the right vocal cord and the right ventricular band. There was no motion of the right vocal cord or right arytenoid. The left ventricular band and the left vocal cord were involved to a lesser degree. There was normal motion of the left vocal cord. There was a small, tender mass palpable in the right side of the neck in the region adjacent to the larynx.

Course in Hospital: The patient was placed on penicillin, 100,000 units intramuscularly every three hours, in addition to sulfadiazine, 1 gm. every four hours by mouth. Gram negative cocci were seen on smear from the epiglottis, but no organism appeared on culture.

On the day following admission, swelling became so painful that the patient had to be placed on intravenous feedings. Examination of the larynx at that time revealed that the epiglottis, aryepiglottic folds and arytenoids were more edematous than at the time of admission. The vocal cords could not be seen, but the glottic chink was visible.

That afternoon the patient suddenly became dyspneic and cyanotic and had great difficulty with inspiration. He coughed up a mucus plug and the dyspnea was relieved. Several minutes later there was a repetition of this incident. The patient was taken to the operating room immediately and tracheotomy was performed. In the course of the operation, he once again had difficulty with catching his breath, but this was relieved immediately as the trachea was opened.

Postoperatively, the penicillin was continued. Sulfadiazine was given intravenously, and penicillin aerosol was started every two hours.

On the day following tracheotomy, the condition of the patient was essentially unchanged. Temperature 101°. Pulse 92. Respirations 22. The appearance of the larynx did not change, but the mass on the right side of the neck was larger.

Two days following tracheotomy, the patient was markedly improved. The temperature began to fall by lysis. The edema of the larynx began to subside so that the edges of both vocal cords could be visualized. The mass in the side of the neck appeared much smaller and the patient began to take food by mouth.

On the fourth postoperative day, penicillin was reduced to 500,000 units every three hours and sulfadiazine was discontinued.

On the sixth day, decannulation was started and intramuscular penicillin was discontinued.

On the tenth day the appearance of the larynx returned to normal and the penicillin aerosol was discontinued. The patient was discharged from the hospital on the seventeenth day after tracheotomy.

Four million, eight hundred thousand units of penicillin were administered parenterally over a period of seven days.

CONCLUSIONS.

1. Early diagnosis of acute infection of the epiglottis is of extreme importance.
2. Examination of the larynx is imperative where there is a history of hoarseness, laryngeal cough or pain on swallowing.
3. The onset of obstruction may be very sudden, therefore tracheotomy must be performed early.

3235 Parkside Place.
140 East 54th Street.

ANGIOENDOTHELIOMA OF HYPOPHARYNX.*

F. E. LeJeune, M.D., and C. H. Steele, M.D.,
New Orleans, La.

Although angioendothelioma is not uncommonly encountered in various portions of the body, it rarely occurs in the hypopharynx, there being only one case recorded in the available medical literature.[1] In the case to be reported, complete removal was made possible by suspension laryngoscopy, which permitted bimanual operative manipulation and excision of the large tumor, subsequently proved to be angioendothelioma. It is believed that no other method of peroral surgical approach to the lesion would have been so successful.

REPORT OF CASE.

G. B., a 45-year-old white farmer, was admitted to the Eye, Ear, Nose and Throat Hospital on March 13, 1943, complaining of dyspnea, dysphagia, loss of weight, and change in voice quality. Dysphagia had been present for about 15 years and was first noticed while the patient was swallowing water. Although difficulty in swallowing continued, the patient soon learned to swallow food and fluids successfully by taking small amounts; however, regurgitation of fluids through the nose frequently occurred. Since January, 1943, it had been impossible to swallow any solid food and little liquid. There had been a gradual loss of 45 pounds in body weight during the course of the illness. Dyspnea, which was first noticed in September, 1942, became progressively worse, until at the time of admission to the hospital the patient could breathe only by inclining the head toward the right shoulder. He slept sitting up with the head so inclined. For the past three years of the illness the speaking voice had become progressively more hollow and was associated with severe phonatory weakness. These complaints had prompted the patient to visit several physicians, but none had been able to account for the symptoms.

Examination on admission revealed a patient, 5 feet, 11 inches in height, in a severe state of malnutrition, weighing 98 pounds. Signs of laryngeal or pharyngeal obstructive dyspnea were present. Frequent raising of moderate quantities of foul-smelling, grayish sputum from the throat was noted. Indirect laryngoscopy revealed a smooth, glistening, grayish mass, approximately 2.5 cm. by 4 cm. in size, nearly filling the

*From the Departments of Otolaryngology, Tulane University of Louisiana School of Medicine and the Ochsner Clinic, New Orleans, La.

Editor's Note: This ms. received in Laryngoscope Office and accepted for publication, July 15, 1948.

hypopharynx. The larynx was not visible and only the upper edge of the epiglottis could be seen. A small space existed between the tumor and the left pharyngeal wall, permitting a restricted airway. No enlarged lymph nodes or abnormalities of the larynx could be found on palpation of the neck. Except for emaciation the remainder of the physical examination was normal. Results of laboratory examinations, including urinalysis, blood chemistry and serology, were negative. A Roentgenogram of the chest showed no abnormality. On the day of admission, a low tracheotomy was done under local anesthesia for relief of the dyspnea. On March 15, 1943, two days following tracheotomy, the patient was again taken to the operating room.

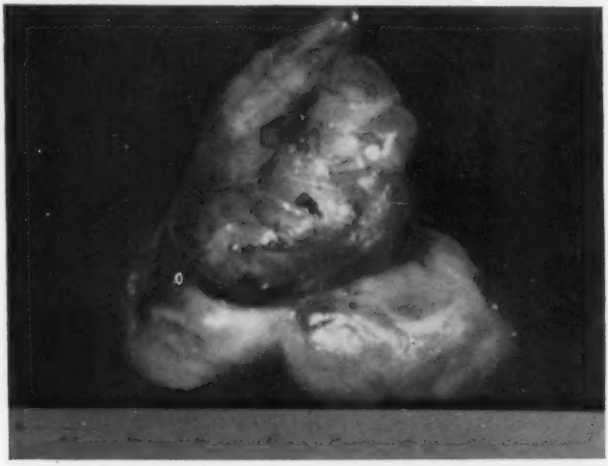

Fig. 1. Photograph, enlarged from 16 mm. kodachrome film, of angioendothelioma of hypopharynx.

Operative Procedure: Under intravenous sodium pentothal anesthesia, laryngoscopy was performed by means of the Lynch suspension laryngoscope, with a small sized spatula attached. A smooth, grayish, lobulated tumor, arising from a relatively small area of the posterior wall of the hypopharynx, was exposed. A large snare was applied about the base of the lesion, but at this point in the procedure apnea developed. Further efforts toward removal were abandoned. Resuscitative measures were immediately instituted and the patient was revived. He was then returned to his room.

On April 7, 1943, the patient was again taken to the operating room. Anesthesia was obtained by the administration of ether through the tracheotomy tube and suspension laryngoscopy was again performed. The tumor was removed by sharp and blunt dissection and application of a snare at its point of attachment to the posterior hypopharyngeal wall.

Fig. 2. Photomicrograph of angioendothelioma showing vascular spaces (×100).

No visible deep extension of the lesion was noted. The resulting defect in the pharyngeal mucosa was obliterated by interrupted sutures of No. 000 catgut after hemostasis had been secured by ligature. The patient withstood the operation well.

Fig. 3. Photomicrograph of angioendothelioma showing cellular structure (×200).

*Pathologic Report:** Gross description (see Fig. 1): The tumor, measuring 2.5 cm. by 4 cm. by 6.5 cm., was lobulated, containing three large

*Dr. Geo. A. Hauser, Pathologist, Eye, Ear, Nose and Throat Hospital, New Orleans, La.

Fig. 4. Photomicrograph of angioendothelioma showing connective tissue elements brought out by Masson stain (×100).

lobes. It was mixed gray and pink in color. The surface was smooth and glistening except at the site of removal. The cut surface was of a soft, fatty homogeneous consistency.

Microscopic description (see Figs. 2, 3, 4 and 5): The tumor consisted

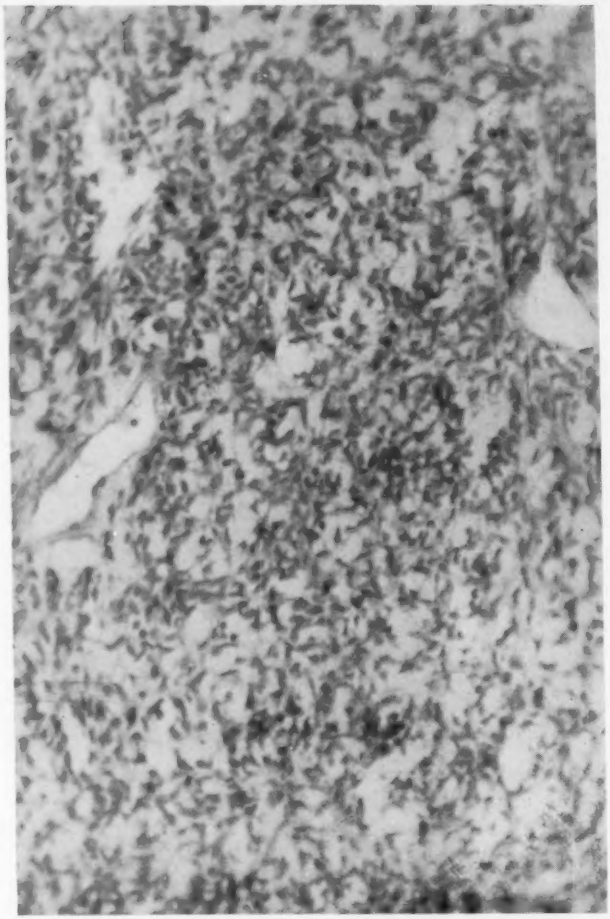

Fig. 5. Photomicrograph of angioendothelioma showing connective tissue elements brought out by Masson stain (×200).

of endothelial cells with a small amount of supporting and surrounding connective tissue. Most of the tumor was composed of sheets of endothelial cells, some of which showed mitosis. There were many small blood vessels and in some areas greatly dilated vasculolymphatic spaces,

some of which appeared to be lymphatics, whereas others contained blood and some were thrombosed. The overlying mucosa showed polypoid hyperplasia with lymphoid and plasma cell infiltration. The surface of the tumor was atrophic.

Pathologic Diagnosis: Angioendothelioma.*

Course: Convalescence was uneventful. Decannulation of the trachea was carried out three days before discharge from the hospital on April 15, 1943. Indirect laryngoscopy revealed satisfactory healing of the hypopharyngeal wound. Dysphagia, dyspnea and change in voice were no longer present. No word has been received of any recurrence of the lesion.

SUMMARY.

1. A case of angioendothelioma of the hypopharynx is reported, there being only one other such instance recorded in the available medical literature.

2. Suspension laryngoscopy facilitated peroral exposure, bimanual dissection, removal of the tumor and repair of the resulting hypopharyngeal defect.

REFERENCE.

1. MANGABEIRA, ALBERNAZ, and DE TOLEDO, R.: Contribuicao ao estudo dos tumores raros da faringe hemangio-endotelioma da hippo-faringe. *Rev. Brasil de oto-rino-laryng.*, 9:267-283, July-Aug., 1941.

*Diagnosis was confirmed by Dr. J. E. Ash, Colonel, Medical Corps, U. S. A., Curator, Army Medical Museum, Washington, D. C.

AMERICAN BOARD OF OTOLARYNGOLOGY.

The American Board of Otolaryngology will conduct the following examinations in 1949:

May 11 to 14 in New York, N. Y., at the Biltmore Hotel.

Oct. 4 to 7 in Chicago, Ill., at the Palmer House.

ADENOLYMPHOMA OF THE PAROTID GLAND.

T. E. BEYER, M.D., and J. R. BLAIR, M.D.,
Denver, Colo.

Since otolaryngologists are showing an increasing interest in diseases of the salivary glands and since the subject of

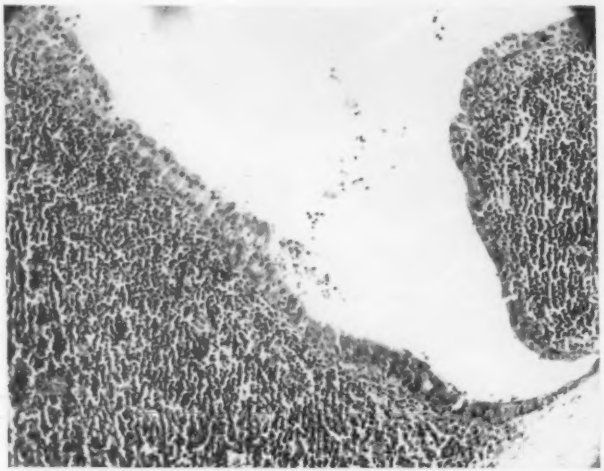

Fig. 1. High power showing tall columnar ciliated epithelium.

adenolymphoma of the parotid finds no mention in our literature, the following case report may be of interest.

CASE REPORT.

The patient, a 55-year-old Japanese male, examined Feb. 7, 1947, stated that a month before, his wife first noted a swelling in front of his left ear. This was not tender or painful and did not limit the motion of the mandible. Aside from enlarging rapidly, it was causing no symptoms.

Editor's Note: This ms. received in Laryngoscope Office and accepted for publication, Aug. 27, 1948.

Otolaryngologic examination revealed no abnormalities. In the midportion of the left parotid gland at the angle of the mandible there was a firm, immovable, insensitive mass which was not fixed to the skin. Steno's duct was patent, and clear saliva could be expressed. There was no cervical adenopathy.

Unfortunately, a sialogram was not done.

The preoperative diagnosis was mixed tumor of the left parotid.

The patient was operated upon, Feb. 8, 1947, under ether anesthesia. The skin incision began just anterior to the tragus and extended to the lower border of the parotid gland. The capsule of the parotid was opened

Fig. 2. Low power showing collections of lymphocytes with germinal centers.

and the gland divided horizontally in its midportion. When the halves were retracted an encapsulated tumor was easily enucleated by blunt dissection. A thin layer of pharyngeal mucosa was apparently all that separated this tumor from the oropharynx. The capsule of the gland was closed and the skin closed without drainage.

The patient made an uneventful recovery and has had no recurrence to date.

The pathological report by Dr. S. K. Kurland was as follows: "*Gross:* The specimen consists of a cystic structure from the left parotid. It measures 4 cm. in greatest dimensions. The wall of the cyst is thin. The lining is somewhat roughened.

"Microscopic examination of the tissue reveals one part to consist of

salivary gland structure, adjacent to which is dense fibrous tissue. In the fibrous tissue are cystic spaces lined by several rows of flattened cells and in some instances by tall, columnar, ciliated epithelium (see Fig. 1). Beneath the epithelium are dense collections of lymphocytes. In these collections are germinal centers. The cystic spaces many times are filled with debris (see Fig. 2).

Diagnosis: Adenolymphoma of the left parotid."

SUMMARY.

1. Adenolymphomata of the salivary glands are being reported with increasing frequency in the surgical literature.[1-4]

2. Clinically, they simulate mixed tumors of salivary glands.

3. The majority of cases appear to be benign, but malignant changes have been reported.[1]

4. The treatment of choice is surgical enucleation. Irradiation has been shown to be of little or no value.

5. Acquaintance with the characteristics of this relatively infrequent tumor may be of value to otolaryngologists interested in treatment of diseases of the salivary glands.

BIBLIOGRAPHY.

1. GASTON, E. A., and TEDESCHI, C. G.: Adenolymphoma of the Parotid and Submaxillary Salivary Glands. *Ann. Surg.*, 123:1075-1089, 1946.

2. HARRIS, P. N.: Adenocystoma Lymphomatosum of the Salivary Glands. *Am. Jour. Pathol.*, 13:81-87, 1937.

3. HAMPERL, H.: Adenolymphoma, Relation to Spindle Cells (Oncocytes. 291:704-705, 1933.

4. FRESHMAN, A. W., and KURLAND, S. K.: Cystadenoma Lymphomatosum. *Am. Jour. Clin. Pathol.*, 8:422-430, 1938.

5. PALMER, A.: Oncocytoma of the Trachea. THE LARYNGOSCOPE, 53:377-382, 1943.

CORRECTION.

In the article entitled, "The Articulation Area and the Social Adequacy Index for Hearing," in the August issue of THE LARYNGOSCOPE (Volume 58, pages 761-778), a footnote acknowledging the assistance of the Office of Naval Research was inadvertently omitted by the author. Actually, most of the experimental studies on which the paper was based and the preparation of the paper itself were carried out under Contract N6onr-272 between the Office of Naval Research and Central Institute for the Deaf.

IN MEMORIAM

JOHN GORDON WILSON, M.D.,

1858 - 1948.

Dr. John Gordon Wilson was born in Edinburgh, Scotland, on Dec. 10, 1858. He was the son of John and Grace Glass Wilson. His boyhood was spent in his native city and he continued his education at the university there, obtaining his M.A. in 1885 and M.B. and C.M. in 1890. Shortly after graduation he went to Europe, where he studied at the Universities of Strassbourg, Berlin and Vienna. Several months of this period were spent at Strassbourg with Dr. Bethe, who was a pioneer investigator in intravitam staining. Returning to Scotland, he practiced general medicine in Glasgow until 1900, when he came to the University of Chicago, where he accepted a Fellowship in Anatomy, later becoming assistant professor under Lewellys F. Barker. It was during this period that he developed the method of intravitam staining with methylene blue and published an article on the taste buds of the larynx.

Since he had no teaching duties in the summer months, he usually traveled to England, where he worked with Dr. Frederick Mott at Claybury, England. During these visits he demonstrated the nerves and nerve endings of the human eardrum, and the antrioventricular bundle of His.

In 1908, he was made professor of otology at Northwestern University Medical School and later became chairman of the Department of Otolaryngology. As stated above, his earlier investigations were in the "Intravitam Staining with Methylene Blue" and series of articles were published in 1909, 1910 and 1911.

Seeking new fields as all fundamental investigators do, he next turned to the exploration of the labyrinth. This was carried out on laboratory animals such as the cat and pigeon. This necessitated long hours after a busy day at the office or

on the week ends. Among his publications were "The Mechanism of Labyrinthine Nystagmus and Its Modification by Lesions in the Cerebellum and Cerebrum," "The Differential Diagnosis of Lesions of the Labyrinth and Cerebellum," and "The Effects of Stimulation of the Labyrinth of the Ear in the Living Animal."

When the first World War broke out, Dr. Wilson offered his services to the Canadian Expeditionary Forces and was sent to Europe as a captain. He saw front line duty and suffered considerable deafness in one ear from the result of exposure

to high explosives. This stimulated him to further investigations and he published several articles dealing with "The Effects of High Explosives on the Ear." After again assuming civilian life, his attention was soon drawn to the petrous temporal bone and the utriculoendolymphatic valve. One of his additions to otologic study was his work in establishing patterns of air cells in the petrous bone, which served as landmarks in the surgical approach to the petrous tip.

Always interested in otosclerosis, Dr. Wilson was invited to give a paper on "Recent Investigations in Otosclerosis" at the International Oto-Laryngological Conference in Madrid in 1932.

Not all his time was devoted to investigative work, as he had a keen interest in medical history. In the summer of 1928 he spent many hours in the British Museum gathering data for his presidential address before the Institute of Medicine in Chicago. This was a paper entitled, "The Influence of Edinburgh on American Medicine in the Eighteenth Century."

Many honors come to Dr. Wilson. He was a past president of the American Otological Society, chairman of the committees on vestibular research and on aural structure and function of the National Research Committee, foreign member of the Madrid Otolaryngological Society, and member of the Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum, and an Emeritus Follow of the American Laryngological, Rhinological and Otological Society, Inc.

Dr. Wilson died Aug. 13, 1948, in his home at Old Bennington, Vt., where he had lived in partial retirement for the past 10 years. He never lost interest in medicine and each Winter since his retirement he returned to his laboratory in Chicago, where he usually could be seen peering into the microscope, searching for something new in the petrous temporal bone.

THE AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC.

The 1949 Section Meetings will be held as follows:

Eastern Section—Jan. 7, 1949, Boston, Mass.

Southern Section—Jan. 10, 1949, Washington, D. C.

Middle Section—Jan. 17, 1949, Iowa City, Iowa.

Western Section—Jan. 29-30, 1949, Los Angeles, Calif.

The midwinter Council Meeting will take place in New York City on Jan. 8, 1949.

The annual meetings of the Triological Society and the Broncho-Esophagological Association will be held concurrently at the Drake in Chicago on April 18, 19 and 20, 1949. A joint meeting of these two societies will take place Tuesday morning, April 19. On the other days the Triological Society will meet in the mornings and the Bronchoscopic Society in the afternoons.

We also call your attention to these dates and places:

American Board of Otolaryngology—May 11-14, 1949, New York City.

American Laryngological Association — May 16-17, 1949, New York City.

American Otological Society—May 18-19, 1949, New York City.

In order to facilitate the coordination of national meeeings, the Bronchoscopic, the Otological, the Laryngological and the Triological Societies are considering a five-year plan of dates and places. By adoption of such a scheme we hope to reduce the traveling mileage and the amount of time away from our offices. For additional information, write to Dr. C. Stewart Nash, Secretary, 708 Medical Arts Building, Rochester 7, N. Y.

HEARING AIDS ACCEPTED BY THE COUNCIL ON PHYSICAL MEDICINE OF THE AMERICAN MEDICAL ASSOCIATION.

Aurex (Semi-Portable); Aurex Model C-B, Model C-A, Model F and Model H.

Manufacturer: Aurex Corp., 1117 N. Franklin St., Chicago, Ill.

Beltone Mono-Pac; Beltone Harmony Mono-Pac.

Manufacturer: Beltone Hearing Aid Co., 1450 W. 19th St., Chicago, Ill.

Dysonic Model 1.

Manufacturer: Dynamic Hearing Aids, 43 Exchange Pl., New York 5, N. Y.

Electroear Model C.

Manufacturer: American Earphone Co., Inc., 10 East 43rd St., New York 17, N. Y.

Maico Type K; Maico Atomeer.

Manufacturer: Maico Co., Inc., North Third St., Minneapolis, Minn.

Mears Aurophone Model 98.

Manufacturer: Mears Radio Hearing Device Corp., 1 W. 34th St., New York, N. Y.

Microtone T-4 Audiomatic.

Manufacturer: The Microtone Co., 4602 Nicollet Ave., Minneapolis, Minn.

Otarion Model A-1; Otarion Model A-2; Otarion Model A-3; Otarion Models A-4 J and S; Otarion Model E-1.

Manufacturer: Otarion Hearing Aids, 448 N. Wells St., Chicago, Ill.

Paravox Models VH and VL; Paravox Model XT; Paravox Model XTS.

Manufacturer: Paraphone Hearing Aid, Inc., 2056 E. 4th St., Cleveland, Ohio.

Radioear Masterpiece; Radioear 45-CM; Radioear Model 45-M-magnetic air conduction receiver; Radioear Model 45-M-magnetic bone conduction receiver.

Manufacturer: E. A. Myers & Sons, 306 Beverly Rd., Mt. Lebanon, Pittsburgh, Pa.

Ravox (Semi-Portable).

Manufacturer: Zenith Radio Corp., 6001 W. Dickens Ave., Chicago, Ill.

Silver Micronic Hearing Aid.

Manufacturer: Micronic Corp., 101 Tremont St., Boston 8, Mass.

Solopak Hearing Aids.

Manufacturer: Allen-Howe Electronics Corp., 150 Main St., Peabody, Mass.

Sonotone Audicles No. 530, No. 531 and No. 533; Sonotone Model 600; Sonotone Model 700.

Manufacturer: Sonotone Corp., Elmsford, N. Y.

Telex Model 22; Telex Model 612; Telex Model 900; Telex Model 1020; Telex Model 1550.

Manufacturer: Telex, Inc., Minneapolis 1, Minn.

Trimm Vacuum Tube No. 300.

Manufacturer: Trimm, Inc., 400 W. Lake St., Libertyville, Ill.

Unex Model "A."

Manufacturer: Nichols & Clark, Hathorne, Mass.

Vactuphone Model 3.

Manufacturer: Allen-Howe Electronics Corp., 150 Main St., Peabody, Mass.

Western Electric Orthotronic Model 125; Western Electric Model 63; Western Electric Model 64; Western Electric Models 65 and 66.

Manufacturer: Western Electric Co., Inc., 120 Broadway, New York 5, N. Y.

Zenith Radionic Model A-2-A; Zenith Radionic Model A-3-A; Zenith Radionic Model B-3-A; Zenith Model 75.

Manufacturer: Zenith Radio Corp., 6001 Dickens Ave., Chicago, Ill.

DIRECTORY OF OTOLARYNGOLOGIC SOCIETIES.

AMERICAN OTOLOGICAL SOCIETY.

President: Dr. Marvin F. Jones, 121 E. 60th St., New York 22, N. Y.
Secretary: Dr. Gordon D. Hoople, Medical Arts Bldg., Syracuse 3, N. Y.
Meeting: New York, N. Y., May 18-19, 1949.

AMERICAN LARYNGOLOGICAL ASSOCIATION.

President: Dr. Frederick T. Hill, Professional Bldg., Waterville, Me.
Secretary: Louis H. Clerf, 1530 Locust St., Philadelphia 2, Pa.
Meeting: New York, N. Y., May 16-17, 1949.

AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC.

President: Dr. John J. Shea, 1018 Madison Ave., Memphis, Tenn.
Secretary: Dr. C. Stewart Nash, 708 Medical Arts Building, Rochester, N. Y.
Annual Meeting: Chicago, Ill., Hotel Drake, April 18-20, 1949.

SECTION MEETINGS.

Eastern—Boston, Mass., Jan. 7, 1949.
Southern—Washington, D. C., Jan. 10, 1949.
Middle—Iowa City, Iowa, Jan. 17, 1949.
Western—Los Angeles, Calif., Jan. 29-30, 1949.

AMERICAN MEDICAL ASSOCIATION, SECTION ON LARYNGOLOGY, OTOLOGY AND RHINOLOGY.

Chairman: Dr. Fletcher D. Woodward, 104 E. Market St., Charlottesville, Va.
Secretary: Dr. James M. Robb, 641 David Whitney Bldg., Detroit, Mich.

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Conrad Brens, 35 E. 70th St., New York, N. Y.
President-Elect: Dr. J .Mackenzie Brown, Box 584, South Laguna, Calif.
Executive Secretary: Dr. William L. Benedict, Mayo Clinic, Rochester, Minn.

Central Institute for the Deaf

NATIONAL RESIDENTIAL AND DAY SCHOOL FOR THE DEAF AND DEFECTIVES IN SPEECH

Approved by Advisory Council of Foremost Ear Specialists and Educators

New fire-proof buildings beautifully located opposite Forest Park. Modern Dormitories and Equipment. Best home environments. Pupils constantly in care of teachers or experienced supervisors.

ORAL SCHOOL FOR DEAF CHILDREN

C. I. D. offers all advantages of exclusively Speech Training and expert medical supervision for both Resident and Day Pupils.
Nursery School (2 years of age) through the Elementary Grades.

ACOUSTIC TRAINING FOR CHILDREN WITH RESIDUAL HEARING

Salvaging of Residual Hearing is a specialty of C. I. D. The Acoustic Method was created here. Group and individual hearing aids used for class instruction at all grade levels.

LIP-READING INSTRUCTION

Private and Class Instruction for Hard-of-Hearing Adults and Children.
Conversational Classes for advanced pupils. Speech conservation stressed.

CORRECTION OF SPEECH DEFECTS

Private and Class Instruction for children with normal hearing and delayed speech or defective speech.
Resident and Day Pupils (2 years of age through Elementary Grades).
Private Instruction for Adults.
Correction of Imperfect Phonation, Imperfect Articulation, Aphasia, Stuttering.

TEACHERS TRAINING COLLEGE

Two years of Training following a professional curriculum for applicants with adequate college qualifications. Graduates qualify for degrees of Bachelor of Science in Education or Master of Science in Education from Washington University. Graduates prepared to teach both the deaf and speech defective.

DR. MAX A. GOLDSTEIN, Founder · MISS JULIA M. CONNERY, Principal Emeritus

For further information address

DR. HELEN SCHICK LANE, Principal

818 S. KINGSHIGHWAY 10, ST. LOUIS, MO.

CONTENTS

NIELS STENSEN (NICOLAUS STENO), 1638-1684. A FAMOUS ANATOMIST WHO EXCHANGED THE SCALPEL FOR A BISHOP'S MITRE. Walter A. Wells, M.D., Washington, D. C. - - - - - - - - - - 1173

ANESTHESIA IN ENDOSCOPY. Joseph W. King, M.D., Anderson, Ind., and David H. Jones, M. D., New York, N. Y. - - - - - - - - 1195

THE LOCAL APPLICATION OF "SULFAMYLON" [PARA-(AMINOETHYL)-BENZENE SULFONAMIDE HYDROCHLORIDE] IN OTITIS EXTERNA AND CHRONIC OTITIS MEDIA. A PRELIMINARY REPORT OF 141 INFECTIONS IN 108 PATIENTS. J. W. McLaurin, M.D., Baton Rouge, La. 1201

BACTERIOLOGICAL STUDIES ON A NASAL DECONGESTANT CONTAINING THE ANTIBIOTIC METHYLOL GRAMICIDIN. Barbara Taylor and Milton J. Foter, Cincinnati, Ohio - - - - - - - - - - - - - - 1206

PENICILLIN IN THE TREATMENT OF DISEASES OF THE EAR, NOSE AND THROAT. Virgil L. Payne, M.D., Pine Bluff, Ark. - - - 1216

THE RATIONAL BASIS FOR THE USE OF VITAMINS IN THERAPEUTICS. Agnes Fay Morgan, M.D. (by invitation), Berkeley, Calif. - - 1230

INFECTIONS OF THE EPIGLOTTIS WITH OBSTRUCTIVE DYSPNEA. (TWO CASE REPORTS.) Bernard Friedson, M.D., and David H. Jones, M.D., New York, N. Y. - - - - - - - - - - - - - - - - 1243

ANGIOENDOTHELIOMA OF HYPOPHARYNX. F. E. LeJeune, M.D., and C. H. Steele, M.D., New Orleans, La. - - - - - - - - - - - 1246

ADENOLYMPHOMA OF THE PAROTID GLAND. T. E. Beyer, M.D., and J. R. Blair, M.D., Denver, Colo. - - - - - - - - - - - - - 1253

CORRECTION - 1255

IN MEMORIAM.
JOHN GORDON WILSON, M.D., 1858-1948 - - - - - - - - - 1256

THE AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC. - - - - - - - - - - - - - - - - - - - 1259

HEARING AIDS ACCEPTED BY THE COUNCIL ON PHYSICAL MEDICINE OF THE AMERICAN MEDICAL ASSOCIATION - - - - - - - - - - 1260

DIRECTORY OF OTOLARYNGOLOGIC SOCIETIES - - - - - - - - - 1262